DB Name	Query	Hit Count Set Name		
USPT,JPAB.EPAB,DWPLTDBD	110 and 111 and 112 and 114 and 117	11	1.18	
USPT.JPAB.EPAB.DWPLTDBD	ampicillin	11779	<u>1.17</u>	
USPT.JPAB.EPAB.DWPLTDBD	110 and 111 and 112 and 114	16	<u>I.16</u>	
USPT.JPAB.EPAB.DWPLTDBD	(phenylglycine amide) or (d-phenylglycine amide)	58	1.15	
USPT,JPAB.EPAB,DWPI,TDBD	(sulfuric acid) or h2so4	186645	<u>1.14</u>	
USPT,JPAB,EPAB,DWPI,TDBD	(sufuric acid) or h2so4	30723	<u>L13</u>	
USPT,JPAB,EPAB,DWPI,TDBD	(d-phenylglycine) or phenylglycine	3390	<u>1.12</u>	
USPT.JPAB.EPAB.DWPLTDBD	enzym\$5	176652	<u>I.11</u>	
USPT.JPAB.EPAB.DWPLTDBD	(6-aminopenicillanic acid) or 6-APA	1962	<u>1.10</u>	
JPAB,EPAB,DWPI	CN-1165032-\$.did.	0	<u>L9</u>	
JPAB,EPAB,DWPI	jp-05204120-\$.did.	2	<u>1.8</u>	
JPAB.EPAB.DWPI	jp-02240026-\$.did.	2	<u>1.7</u>	
JPAB EPAB DWPI	jp-05204120-\$.did.	2	<u>L6</u>	
JPAB.EPAB.DWPI	jp-5204120-\$.did.	0	<u>L5</u>	
JPAB.EPAB.DWPI	jp-2240026-\$.did.	0	<u>L4</u>	
JPAB,EPAB,DWPI	cn-1165032-\$.did.	0	<u>L3</u>	
JPAB.EPAB.DWPI	cn-1165032-\$.did.	0	<u>L2</u>	
JPAB.EPAB.DWPI	cn-1134306-\$.did.	1	<u>I.1</u>	

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APEL:

A newel Anglodiling ester of the meneral formula ##8TBl## wherein B.sur.l represents a nyurogen atom, a methyl group or an anyl group, and B.sub.l represents a hydrogen atom or may be taken together with R.sub.l to form a divalent parbon phain residue, or its acid addition salt.

ABBL:

The hovel <u>Amplicating</u> ester or its avid addition salt is prepared by "I has "ind a prospectation of "Many and ind a prospectation of "Many lamino periodillaring and "Il" or its salt with a compound of the formula ##STRI## wherein R.sub.1 and R.sub.2 are as defined above, and Missia native atom, in reacting a compound of the formula ##STRI## wherein R.sub.1 and R.sub.2 are as defined above, or its acid addition salt with a corresponding parboxylic acid (VI) or its reactive derivative, (2) thereafter, if required, when the resulting compound has the protected amino group or the group convertible to an amino group, deprotecting the protected aning group or converting said convertible group to an amino group, and "B; if further required, converting the product to an acid addition salt.

Aleiti:

The present invention provides also an antibatterial agent comprising the movel <u>Ampioillin</u> ester and a method for the treatment of infectious disease.

BAPR:

This invention relates to novel <u>Ampicillin</u> esters, processes for their production, and to an antibacterial agent comprising such an <u>Ampicillin</u> ester.

B.11 B:

Amilianness are converged colling to alread by anylating the aring group of the area of any the area of is a synthetic period line which is effective in oral administration. Absorption of Amilians from the directive tract, however, is not sufficient, and this are socially twenty and instruction of large traces for optaining the required concentration in blood, which in turn causes increased side-effects.

80000

To person since a plant of <u>verpital in</u>, an attempt was made to a nower Applicable to an estative period for thereby improving its absorpt in it is the outset and tract. For example, <u>Applicable</u> pivally expectly estation for an expectation, and <u>Applicable</u> pithality estation. Talenguallin; see Fritish Fat. No. 1,504,000 gives comparable block <u>Applicable</u> consentrations in oral administration to those obtained by intramus of a siministration.

Parr:

It is an object of this invention to provide novel $\underline{\operatorname{Ampi}(n)}$ descens a their and addition salts.

: 'E :

Another the first the distriction is to all hovel and more beneficial

Fig. 1. The ten decay to the drop of railly ambhastamie known $Arg_{\frac{1}{2}}(x,y,x)$

This another die to the convention is to provide note. <u>Any collines</u> which are noted that extended in the convention thur the intestinal tract, maintain a high concentration in block over longer perious of time and are less towing than known <u>Apportillin</u> ecters such as i di mpi nalilin.

activative and electrical than anyents in a city particle gar necessarily against that

B. 11 B :

A further offers of the convention is to provide a novel gregors of a production of the novel Argunillan esters.

B-111 B-11

Actor did to the agent, these orients and airantares are a dieved by Apply well provides to the memoral formula ##ATR4## whorein Rusubul represents a my are denoted by a freelby, driving of an argic driving, and bused in represents a nyar den at m, or may de taken together with Bischill to firm a sivalent carbon quain recours, or their and addition salts.

POFF:

Specific examples of preferred Ampinglin esters of general formula (I) are:

BUFB:

The acid addition salts of these Ampicillin esters are, for example, salts of these esters with increaning acids such as hydrochloric acid, hydrobromic acid, hydricdin anid and sulturing anid, or salts of these with organing anids such as outrio and and tarterio anid.

BOYER:

Investigations of the present inventors have shown that the <u>Ampicillin</u> esters or the about addition calfor there is have very desirable properties as graphas windle.

E- 11 E

Specifically, in stall administration, the $f(x_1)$ splits esters of the invention are easily arother from the disestive tract, liberate $f(x_1)$ splits in viv., and maintain a might $f(x_1)$ such a neutration in block over 1 no periods of time.

For example, thirty minutes after small administration in mixe, $\underline{\text{Amplicitive}}$ -mothyl-1- wh-1, -si while-4-yi mothyl ester hydromicride and Arginillin - who end not be now to be by mothyl copies hydrolline and element Ampibulluh buhbentration in blood about bitimes as high as that attained by the administration of Argonillin and about 1.5 times as high as that attained by the administration of Argonillin phthaligh ester, and the high Argonillinconsentrations in Flood are maintained over a long period of time. See Experiment I given hereinkelow.

The following section is a marked by the Anglica and extension this invention is a section of the following section of th

B.11 B :

link mark not ingan omning of Aggiorizzon o emetingle. Elw el, sedic wolene4-ylonetny elmen igan omo not sant Aggiorizzon elm elegikingle), sedic wolene4-ylonethyl elmen igan om osobellin vintolated familia and interminal orintes are an orione valde of that of enginesis graph that says a tensor are Englanded System in the

nerennael w .

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If we also note with at the $\frac{\text{App}_{x,x}}{\text{App}_{x,x}}$ extermed the invention have lower with y and $\frac{\text{App}_{x,x}}{\text{App}_{x,x}}$ with the invention has a sum of y.

BUFB:

Experiments 1 to β are described below for demonstrating these advantages of the $Antileo_{i+1}$ extens of the invention.

B : : :

Factor to the few to opposite was raily laminaters to in a case of the particle of the second of the week of miles any, bory weight about the particle of the particle of the amount is equivalent to the mile of a composite animals periodically, and the concentration of Ampirollin in the second was measured by a bicassay method. The blood Ampirollin level ratio was calculated from the following equation. ##F.VI##

F377F:

The results given in Table 1 clearly show that the compounds of the invention show a high block <u>Anglodding level</u> over a longer period of time than the known pathology, esternic.

1311:

Frodrugs such as Americallin bivalovlowymethyl ester or Americallin phthalidyl ester have been known as orally administrable Americallin. The ester group of the Americallin ester of the invention (i.e., (2-oxo-1,3-dioxolen-4-yl)methyl group) is shown by a formula below in comparison with those of the known prodrugs.

BOFF:

It is clear therefore that the ester group of the Ampicillin ester of the invention pite differs from those of the known Ampicillin esters. It is surprising that the Ampicillin esters of the present invention have the attresaid excellent properties as pharmaceuticals over these known Ampicillin esters.

BSF5:

According to one process of the invention, the Ampicillin ester or its acid addition salt of the invention can be produced by reacting a compound of the general formula **STRS** wherein A represents a protected amino group or a group convertible to an amino group, or its salt at the carboxyl group with a compound of the general formula **STRS** wherein R.sub.l and R.sub.l are as defined above, and K represents a halogen atom, and if required, when the resulting compound has the protected amino group or the group convertible to an amino group, eliminating the protecting group tron the protected amino group is converted amino group the group, and if further required, converting the product to its acid addition salt.

222

A compound corresponding to beneral formula (II) in which A is a free amino droup is a conjound well known as <u>Amplicition</u> and readily available common traility.

B.11 B :

Acting unally, the compound of peneral formula (11) can be produced by converting the tree among group of <u>Ampicullin</u> to the group A (in this case, the group A is desirably a protected amino group).

BSFR:

The compound of momenal formula (II) can also be produced by reacting examinopolicitization for its salt at the carboxyl group with a carboxylic and in the firstly ##JTEll## wherein A is as defined hereinaboxe, or its reactive because of the carbox will approve for producing the

ring that is formulated by the sweet field, is example, in Mark Bata Model, in (0,1)

B. 11 B :

inus, the $\frac{Annothing}{Annothing}$ ester of general termula of or its acid addition salt is formed. The acid addition salt is prepared by reacting the $\frac{Annothing}{Annothing}$ ester having a free among though of general formula of with an acid, for example, an inorganity acid such as nyunoshlorib acid, hydriching acid, hydriching acid, and $\frac{Annothing}{Annothing}$ or an organity acid such as other acid, or tartering acid.

9.11.9

According to preferred end alments of the process of the invention, there are provided a process for producing the <u>Applicable</u> ester of general formula. It is the according to the according a compound of deteral to the according to the According to the process of a continuation of the process of the process of a continuation of the process of the according to a process for producing a mineral acid salt (e.g., hydrochloride, or the <u>Approicing</u> ester of general formula (I) which comprises reacting a compound of general formula (II) in which A is an amine group in the form of a mineral acid such as hydrochloride, with the compound of general formula (III).

1.1

Assirting to another process provided by the invention, the Amginilin ester of general formula 1, or its acid addition salt can be produced by reacting a compound of general formula ##STR13## wherein R.sub.1 and R.sub.2 are as defined above, or its acid addition salt, with a carboxylic acid of the general formula ##STR14## wherein A is as defined above, or its reactive derivative at the carboxyl group; thereafter, if required, when the resulting compound has the protected amino group or the group convertible to an amino group, eliminating the protective group from the protected amino group, or therefore salt there is a salt to exercise the carbox required, the error is a salt and animal salt thereof.

1. 1: 1. .

The former can be performed preservably by reacting e-aminopenicillanic acid or its salt at the carboxyl group with an equimolar amount, or a molar excess, of the compound of peneral formula. III in an inert organic solvent such as tetranyoroturan, droxame of acetone in the opticual presence of a base (when deaminopenicillanic acid is used, the presence of a base is preferred) at a temperature of from about 1.degree. 2. to room temperature.

PSFR

The latter can be performed preferably by reacting depicted and pencillance and as exampled as exampled about the amino group at the deposition protected as the deposition protected as a deficit lase, or its sale at the carbodyl group, for example explosive amino acid benegleposition, with the compound of according tormula (III) under the same obtainings as in the directed aminopenical lands acid process, thereasive reactions the resulting expressed aminopenical lands acid ester with phosphorus pentachloruse and a lower alockel such as methanic at the temperature of my lower states on the presented in their acid as the temperature of my lower about a presented in the same compound such as Merotopic spicing, procedure and tractifications, and there after testing water to a second of the resulting process.

4 of 10

The reaction between the our point of deneral formula V or its additable in all than the same V_{ij} and V_{ij} and it deneral formula V_{ij} or its feathive declinations V_{ij} and V_{ij} when the sumpound of r in the TV char again twitter amind group or a in up of ivertible to an amin droup, the protecting group is removed from the protected aming group, or the himperiable group is honverted to an amino group and if desired, the groups of inverted to its arms addition salt. Thus, the Empirical ester of general normala. Il or ity and a apptitude salt iz flared.

Annual not operate represents of the above proceeds, there are provided a growledd for global that the <u>Argadal</u> in ester of deleral formula (1) of its atla-armiting out unigher regulated twa timb a compound of general formula (VI) in which A is a shift base group or an enamine group with the compound of general formula (V), thereafter converting the Schiff base group or the enamine group (A) of the resulting compound to an aming group and if required, reinverting the product into its about addition salt, and a probess for producing an acid addition salt, such as a hydrochloride, of the Ampio ester of general formula (1) which comprises reacting a compound of general formula (VI) in which A is in the form of an acid addition salt such as a Eggin while high with the orange underformeral formula ${\mathbb M}$.

B23B:

After the reaction, the $\frac{Anclorillin}{A}$ if general formula (I) or its acid addition salt can be isclared an injurified in a systemany mapper

ESPR:

The Ampibillin ester of general formula (I) or its pharmaceutically acceptable acid addition salt is converted back to Ampicillin in vivo when administered to an animal. Accordingly, this invention also provides an antibacterial agent simprising the Amplicillin ester of general formula (I) or its pharmaceutically assertable as in addition salt as an active ingredient.

B.11 B:

The antibacterial agent of this invention may consist only of the <u>Ampicillin</u> ester of general formula [I] or its pharmaceutically acceptable acid addition sult, or a mixture of it with a pharmaceutically acceptable carrier.

The pharmaceutically acceptable carrier may be those carriers which can be used in formulating <u>Ampipillin</u>. Examples are starch, lactose, hydroxypropyl well lives, onystalling well-livess, namesium stearate, and calcium stearate.

B 3 F B :

The antibarterial tent of this invention is administered to man and other animals on a loss of $1.05\,h^2$ ma ky body weight day calculated as the arthogologic esternologic consiste pharmacountrially as extable solt.

Bischill byarten,

Harama:

 $\frac{2m(1)!}{1!m}$. For the hory l=1 , l=di explained by limiting less than E. sub. Lapheny l , l=di and l=d and l=d and l=d and l=d

posibling, , }= set invlic wy-d-cyslshewen-l-yl ester (B.sub.l and B.sub.) Bether form the on up == H.sub., ==.sub.} , wi

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omportus of subject and objects by the ordinal Helphon there. But do I are Bus do 2. To detail for the ordinal poles Musical Elements do 2.

B. 11 11:

A. Appropriate femethy: -1, 3-diswelen-4-yl methyl ester hydrochloride compounds of the invention

1. 1711.

For $\underline{R}(p)$ ($\underline{r}_{1}, \ldots, \underline{r}_{n}$) of Equation 1. The second was enterptically described and \underline{r}_{1} and \underline{r}_{2} is the substitute of

· :

Is $\underline{k(1)}, (1), (2)$ paths. The ester hydrochloride of a known compound used as a control, see Fritzen Fata M . 1, 204, 60.

F-211 ":

Applicable triby materials wherein

P. . . . :

TABLE 1 | Item Ampisillon Level ratio | The Line of Florid Taking min. Of Compound 18 31 60 80 120 180

BSTL:

Ester group

Ampicillin pivalcyloxy methyl ester

##STR5## Ampicillin phthalidyl ester ##STR6## Ampicillin ester of the
invention ##STR0##

1 H. H. H. :

Ambiguous trinymate in ong was inspersed in eight of dimethyl formamide, and lot more preassium hydrogen carbonate was added. The mixture was occled to lifetime. It and stirred, beneal Hehyde I.M ml was added, and the mixture was stirred at I.degree. C. for 1.6 hours. Then, 126 mg of potassium hydrogen carbonate and 320 mg of 4-bromomethyl-8-phenyl-1,3-dioxolen-2-one were added, and the mixture was further stirred at 1.degree. C. for 3 hours.

Water [1] mil' was aided, and the mixture was concentrated under reduced pressure to distill our aperonicitie. The aqueous layer was repeatedly washed with ethyl aperated, and saturated with sodium chloride. The separated oily substance was extracted with 50 ml of mothylene chloride, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfato. The dried craunic layer was concentrated until the amount of methylene chloride decreased to one half. Isopropyl alcohol [30 ml) was added, and the mixture was again concentrated under reduced pressure to give a colorless solid. The solid was collected by filtration, and washed successively with isopropyl alcohol and ether to give 320 mg (yield 46.4) of [Minimus.lab. of with the prophenyle], reduced and ether to give 320 mg (yield 46.4) of [Minimus.lab. of with the color of the color o

. 21.3

The resulting $\frac{Approximate}{Approximate}$ ester hydroful ride was incubated in 40 mouse blood in pH 0.4 phosphate buffer at 30 degree. 3. for 10 minutes, and then subjected to bloautography. It was found to be completely converted to $\frac{Amproxillin}{Amproxillin}$.

DEFE:

Employment tringerate of the was abstrace in more fire tripler manife, and the model of present and constructed was a left of the model of present and constructed was a left of the model of the model

rd of 4-spp restry. - -restry: -1, :-if x len-l- ne were alsei, and the righterwas therea at the green that roth grow After the reaction, the reaction must bee was policed unto the water. The presign area about was extracted with to must be thy, and take the ordanist cayer was washed with to mission water threetures, and dried Wer annydr us radieslar solitate. The ethyl eletate was distribled off under reduced pressure to give a yellow syrup. The resulting syrupy residue was dissolved in 4 ml of abetonotile and the solution was abjusted to pH ... with bilute hydrochlipic acid. The solution was then stirred at literree, in the binder. Water I fill was area, and the about filles was about 10 fills was about the filles was cause to repeate thy with ethyle abetate, and the hosat material and scalar billions as The organist of only object and expansion as the position of the free injuries on, or per, and was need to the association as a total organise of the free injuries. calum only rise. The methylene only notes layer was about over annyar us a glom solitate, college; and consentrated under respond pressure to one half or its volume. In the solution isopropyl alcohol .30 ml was added, and the mixture was again contentrated under reduced pressure to give a colorless amorphous solid.

11255:

The solid was collected by filtration and washed with isopropyl alcohol and when to dive 31, our yorld 82.6 of <u>Ampicillin</u> energyle, excellent acquired eylopethyl espen by in objective as a collected

worms as a confine project railther of wing properties.

The resulting $\frac{2\pi r^2 + r^2}{2\pi}$ ester hydrophloride was incubated in 40% mouse blood $\frac{2\pi r^2}{2\pi}$ and then subjected in pH 7.4 phosphate buffer at 37.degree. C. for 10 minutes, and then subjected to bicautography. It was found to be completely converted to Ampicillin.

By the same method as shown in Ewample 1, (2 , 180 mg of Ampirillin ..., i- parkenyl (i.xy-.-ry dehexenyl) ester hydrochleride was ebtained as a ouloniess aborgo ús siliú from 2 g if <u>Argloillin</u> tribydrate and 1 g of t=broms=1,v=sarbonyldickytytichemene (yield 1 .v.).

DEFR:

The resulting Ampicillin ester hydrochloride was incubated in 40% mouse blood in pH 0.4 phosphate buffer at 37.degree. C. for 10 minutes, and then subjected to bicautography. It was found to be completely converted to Ampidillin.

Among this parameter is a was dispersed in 0.4 ml or dimethyl formamide, and a function assign by it can happen are was acted. The mixture was cooled to ideare. N., and 1 ml is penualdehyde was appled. The mixture was stirred at lideares, to fideares. Of for 3 hours. To the mixture were added 500 mg of potassium hydroden parbohate and 1 g of 4-bromomethyl-1,3-dioxolen-2-one, and the rixture was etimed at 1. Semes, to 5. Semes, 1. In 6 hours,

DEER:

Water [1] ml was added, and the mixture was tenentrated under reduced pressure to remove agentifie. The appenus layer was repeatedly washed with enhyl a menare, and samuraned with sodiub obligation to precipitate an oran me our-like substance. The appeaus layer was non-red by decantation. The dom-like coderance was ones lived in cottancl, decal criced with activated carbon, cooled to the new N_{s} and proposition to with really stimed other to precipitate a pale frame solin. The solin was collected by filtration, and washed with a mixture of ether and methanol to give $\theta^{(i)}$ mg (yield $0\theta^{(i)}$ of <u>Ampioillin</u> Chewa-1, 3-diawalan-4-yl/mathyl aster hydrochloride as a pale crange amaryh us solii.

DEFE:

The resulting <u>Apply Clin</u>ester by in this rife was in mbated in 40 marse block on the resulting Apply Clinester by the first of the property of the suite of the first of the

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organistics, and the first specifically decreased the control of the traylors of the rest of the war of the first terms. It, and by passing by the decreased that the property of the property

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1 5 5 5 1

After the reaction, the solid was separated by filtration, and the filtrate was incentrated in ter reduced pressure. The resulting syrup was also then in water, and washed with ethyl abstate. The aqueous layer was saturated with solid modulate, and the separated ally substance was extracted with nethylene modulate. The extract was washed with a saturated appears solution of sodium shibrings and some entrated until the amount of methylene chloride decreased to half. Upon addition of isopropyl alcohol, a colorless solid was precipitated. The solid was collected by filtration and washed with isopropyl alcohol and ether to give 132 mg (yield 54*) of Ampicillin (5-methyl-2-oxo-1,3-dicxolen-4-yl)methyl ester hydrochloride as an amorphous solid.

1 EEE:

From . The resulting ester hydrochloride and 95 mg of Tele-sphenylg yould misside hydrochloride, 145 mg (yield 56) of <u>Ampidillin</u> velx. Helphenylel, Helioxolen-4-ylomethyl ester hydrochloride was obtained as a colorless amorthous solid.

TEFF:

Five grams of (5-methyl-2-cxc-1,3-dicxclen-4-yl)methyl <math>(6-amin.penicillana+eptoluenesulfonate was suspended in 300 ml of ethyl acetate. To the suspensionwas added at 1.dearse. T. 170 ml or a . aqueous solution of sodium hydrogen tare pare to thei with its. The mixture was rigorously stirred. The ethyl and are layer was segurated, washed with ice water, dried at C.degree. C. over apply in this mannes into sultate, and concentrated under reduced pressure to give a pale yellow syrup. The syrup was dissolved in 50 ml of methylene chloride. The solution was cooled to ".degree. C., and 1 g of potassium hydrogen carbonate and 2.1 g of 2-1-phenylplycyl chloride hydrochloride were added, and the mixture was stirred at C.degree. C. for 4 hours. After the reartion, the lustible material mag sevarated by filtration, and the filtrage was concentrated under reduced pressure. The resulting syrup was dissolved in water and washed with ethyl abetate. The aqueous layer was saturated with sodium chloride. The separated oily substance was extracted with methylene unicalide, washed with a saturated appeaus solution of sodium chloride and inted for adoptions soliton sulfate. The intel solution was concentrated under rease appressible intoletic arount of methylene chloride decreased to one half. lsopolypolacion i was alpai, and the disture was arain isobentrated under is fire dipressure to drive a collecter solid. The solid was collected by the translation of Appropriation to the solid properties of problems of the solid Appropriation of the solid problems. amorphous solide

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An ethan is solution of the hydroxypropyl religious was prepared and added to the $An_{1,2}$ by lower hydrothic rise and last sec. They were kneaded, extribed this outcomes one hydrothe in the manufest.

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were fire a and top distes to fire a tablet.
our Production of Angloculus Cultivate Represión 1.3-au x len-4-yl metnyl exter
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Finduction of Ampicallin (2,6-mail myldicky-u-myalchemeny) -ester
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-21 Production of Amplifillin (2-exc-1, 3-dioxolen-4-yl/methyl ester)
mydig thi ride
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4 Erodumila of <u>Appidilla</u> Semethyleletwoel, Hedioxolene4-ylimethyl ester
mydrodiloride.
DEFU:
Froduction of Amginillin (2-owo-5-phenyl-1,3-dicwolen-4-yl)methyl ester
hydrochloride
DEFO:
    Froduction of Ampicillon (S-methyl-1-oxo-1,3-dioxolen-4-yl)methyl ester
. . . . . .
                                                     (1) Ampicullin (5-methyl-2-oxe-1,3-
dioxolen-4-yl)methyl ester hydrochloride 356.7 mg Lactose 38.3 mg Magnesium
stearate 8.0 mg 400 mg in total
.10 <u>Ampibillin</u> .5-methyl-1-oxb-1,3-3H-
oxbled-1-yl methyl ester hydrobilloride bid. 0 my labouse 613.3 mg
Equal was a yill be also we have for a 1, \gamma , and finite \hat{x}
Anglorillin Sementhyledechoel, Sedie oxoleneepyl nethyledechoel hydrochloride obt. Ung crystalline cellulose lid ug
lactose [28.3 mg Hydroxypropyl cellulose 10 mg Magnesium stearate 5 mg 800 mg
11: 1.141
1. An argument of the formula ##Clbs (## wherein b.sur.) represents a nymore martin, a methyl in quot an argument, and b.sur. represents a nymore martin or may be taken to sether with b.sub.1 to form a divalent cash m
thann residue, or a pharmaceutically acceptable acid addition salt thereof.
MER:
\star . An antibarterial agent comprising an antibarterially effective amount of an Approximation ester of the formula ##STR3 ## wherein R.sub.1 represents a
Egiptien aftr, a rethyl group or an anyl group, and Pisubi. Represents a
Egiptien attr or magine taken transform with Risubil to form a divalent case n
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v. A process for the treatment of bacterial infertious disease which comprises authorstering disease which comprises authorstering disease, the a patient in need there is an <u>Argonical</u> esternic the discussion selection and representation by a methyl or upon an argonic of population. Selection and the argonic end at room payment assent the there with F. a. It is in a division to said there is.

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Instruments in relates to a an improved process or preparation of useful all and an electronistics of parent aming useful all and an electronistics are agent.

F. Y. F. :

Today, semisynthetic beta--lastam derivatives such as ampirillin, amowing lin, seration, sephalexin, sephadroxil and sephalogly sin are, in an industrial scale, prepared by shemical methods, for example by reacting an amino beta--lastam such as 6-aminopenioritanic acid, usually having its carboxyl group protected, with an activated side chain derivative, followed by the removal of the protecting group by hydrolysis. For example, ampicillin e-D--alpha--amin phenylasetamido-penicillanic acid) can be prepared by the time fields, having a suitable protected carboxyl group, with time fields, having a suitable protected carboxyl group, with time fields. These reactions typically involve castly steps soon as sub-series across felicias charitans and organics like methylene filleride and silviation reasons.

FSER:

Within the last years, there has been an increasing amount of publications of cerning the providility of enginestic preparation of periodilins and oppose provide the provide the modern and the parent area. The example, and the results and the parent area. The tast of the example, engines, and the control of example, engines, production of approviding to a state and a Dephenyleadyoine derivative earth as a lower alkyl estern is known from West German patent application having publication No. 1,163,780, Austrian Patent No. 243,486, Dutch patent application No. 70-19138, West German patent application having publication No. 339,761 and interest application having publication No. 339,761 and interest application having publication No. 339,761 and

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The emotion of a volation of an amino distance law an with an applicant agent may be performed in the prevence of a soltance aminase of applice whereby the profite foreign and respect amino distance and the object and an applicable on a voltance of a solution and an interest and an applicable of a voltance of a voltance of a voltance of a voltance of the object and a voltance of the pener parent object and a voltance of the O-NH. Solution of the object parent object and a voltance of a voltance of the O-NH. Solution of the object parent object and are an applicable in

F. 11 F :

In this process is performed at these, it has been about the third at the sections of the reaction, an intreaction arount of the anomal interaction is time, the amount of the fall-law and entraction mixture is a preasing. The decomposition of the theta, where it is formed may be due to hydrolysis thereof whereby and otherwise the and the abid form of the applating agent is formed. In addition, the encycle present may decomplete starting agent about an arent.

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11.11

It has now, surprisingly, been found that improved process conditions are stained if the <u>compacts</u> anylation of the amine obeta. Hastam is performed at the staintly hour contrations of both the parent amino obeta. Hastam and the concept bound anylation agent. Frederically the concentrations of the parent about the parent and obtained application agent are no merithan a protein by no merithan effect the lowest value of a third saturated concentration of the parent amino operated was and of the saturated concentration of the corresponding adulating agent.

1888:

The .beta.-lastam derivative formed may precipitate during the reaction and, a.s., the arid form of the adylating agent such as 1-phenylglycine and 1-phenylglycine may precipitate. Hence, in some cases the reaction number which is a clumy through the reaction.

18.18:

The (parent amino .beta:-lastam has a free amino group which is asylated by the reaction apporting to this invention. The amino .beta.-lastam may conveniently be https://doi.org/1-ACCA. THACCA, THACCA, THACCA, THACCA or THACCO.

DEFR:

The amino .Neta.-lautam, for example 6-AFA or T-ADDA, used in the process of this invention may be obtained by encymatic hydrolysis of the fermented penicillins or sephalosporins, for example penicillin V, penicillin C or sephalosporin C or their ring enlarged analogues of the hydrolysis by-product, if desired (phenoxyacetic acid etc.). Advantageously, the crude solution can be used directly without further purification or dilution.

DEFR:

The adylating agent may be in an activated form. Preferably, the adylating agent is an amide or an ester. The adylating agent may be a derivative of Tephenylplydine, Tephenylplydine, Tephydroxyphenylglydine, Del,5-dihydrophenylglydine or mandelid adid, such as a lower alkyl ester methyl, ethyl, negropyl or isopropyl ester or an amide which is unsubstituted or substituted in the edulating agent may be used in the form of a salt, for example, the nymodil ride salt or the H.sub.l Sc.sub.4 salt. The adylating agent may be added in an active form or the active form may be formed in situ.

TEFR:

The solubility of the adylating agent such as the D-phenylalycine or lepthy in applicable increasing will vary with the identity of the solubility of the solubility of the hydrochloride salt of the solution, as well as on the pH value and the temperature of the solution. As a further example, the solubility of the sulphate form of D-phenylglycin amide is about 3.3 M within a pH range from 0.5 to 6.5.

DEER:

Framples of .beta.-lactam derivatives that may be prepared by the process of this invention are appropriating amorabiliting peraction, dephaloxin, dephaloxin, ephaloxin, ephaloxin, ephaloxin, ephaloxin, ephaloxin, ephaloxin, ephaloxin, exploration, ephaloxin, exploration, explo

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The <u>chappe</u> to be used include process of this invention may be any <u>encymental property in the reaction on passions from encymes have been known since an unitable. Fingures to be used are, for example, terms i peniculling and hase of peniculling anylase and classified as E.C. 3.5.1.11. A number of microbial</u>

converge are anomal to have this activity, believed in a for example Acet ragger, Algalization, Eastern make, Myorgiana, Frotamin ragger, Aeromonas. West German patent application having publication No. 2, loc, Thouseholden no. 3 4 core. Flaviburerium lutum patent application No. 7 - 91-8 , Appar cladium, Tepha. Sportum West German patent application naving publication No. 2, 71, 81c., Areticalize pasteurianum, Algalizenes caeralis, f House the Library Marker Company of the Company o of the , wither sear, the content of which is or or crared by reference.

The state of the first transfer of the state the trade have Cuper harpweeks. Freieraply, as $\frac{1}{2}$ deciding a symmetric hard section of a symmetric for a consisting of a gelling polycarbohydrate and a polymer containing tree amino proups, is applied.

The suitable pH value depends, inter alia, on the type of the embyme used. Tain; Part at Shis coli <u>thryma,</u> the pH value is typically in the range from the spectrosity in the range from the propertion of am widilion, a fill value in the range from 1.8 to e.4 is preferred. Control of the (H. Value may be used.

7818:

Suitable encyres on mentrations have be from 1 to 100 U/m1 of U he onit of emagree and inity, see hellwh.

Thing the problem are rither to this invention, an extraprimary high molar rationist week the amount of lietal-lam amover inative which can be seen teres. and the total amount of abordoom of the anylating agent can be brained. Installifum ratio, are outsined using the teachings of this invention and properly resenting the concentration of the anylating agent, the ratio between the conventration of any ating elect and the starting amino legts. He are my the pH value and the endyme. Thus, a ratio or 2.4 was obtained in Frample 1 below using the process of ring to the present invention. In a comparative but the process, vide Example 1 kelow, a molar ratio of only 1.4 was obtained. In addition, the yields of isolated product obtained in this example were 40 and er , respectively.

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The equipment for this experiment consisted of see FIG. 1 a thermistated restor having a volume of 1.8 liters, equipped with a three-flated inpolled and a slew with slots lessons system using 4 M sulphaped as titrant. A valve was positioned at the cutlet of the reactor. The cutlet of the valve was connected via a pump to a basket pentrofuge equipped with a polypropylene may having a density of 1-6 union. The cutlet from the centrofuge was connected via a pump to a feed tank equipped with a stirrer and a glass sinter bottom. The cutlet from the reactor.

1 6 6 6 :

A mixture consisting 1-HFOM toll 4, 100 mmil and e^{-AFA} 40.0 g, 100 mmil in the mixture was added to the reactor with the bottom value closed. The stirring was started. Immobilized Peninchlin 3 acylase (2016) T, side all-following made up to 101 ml was added to the reactor. The pH value was maintained at 6.1. The reaction temperature was about 20 degree. C. Under these conditions, the reaction mixture was almost saturated with D-HFGM and e^{-AFA} . Then, the bottom value was opened allowing the reaction mixture from the reactor to enter the centrifuge. Thereafter, the mother liquor from the ventrifuge was pumped into the feed tank wherein D-HFGM (21.7 g, 120 mmol) and e^{-AFA} 1.1 g, e^{-AFA} much were loaded. The total volume of the suspension in the feed tank was kept at about 75 ml. A flow of about 100 ml/min was maintained in the system. The concentration of reaction components in the reactor, in the reactor outlet, in the centrifuge outlet, in the feed tank and in the feed tank outlet were monitored by analytical HPLC.

CEER

As the reaction proceeded, the amoxicillin and D-HPG formed started to precipitate out of solution. The crystals were separated from the immobilized capture particles by the bottom sieve in the reactor and the crystal suspension was left to the correction where the crystals were separated from the mother tiple. A much the correction was now an essablication with respect to L-HPCM and r-AFA, passwalthrough the feet tank, some of the solid D-HFCM and c-AFA present dissolved such that the cutlet from the feed tank contained saturated D-HPCM and r-AFA. When the total concentrations of D-HPCM and c-AFA came down to about 225 mM HPGM and 215 mM c-AFA, more solid substrate was added to the feed tank. At intervals the crystals in the centrifuge were washed with water, the washing liquid was added to the reactor. The amount of water used was sufficient to keep the volume in the reactor at its starting local troop washes, the company of the contribute was applied.

rung.

After about 12 hours, the desing of D-HF3M and ϵ -APA was stopped. After 14 hours, the ϵ -APA concentration reached 10 mM and the reaction was stopped. The amounts of reaction components are given in Table 1, below.

A comparative experiment was performed at batchwise conditions and the coastion was stopped at the moment where the optimum yield of amoxicillin was retained to home. The reaction temperature was about 10 degree. I., the pilotope was about 10 degree. I. the pilotope was about 10 degree. The plants of the encyme, mentioned in this example above, was used. The total volume of the reaction mixture was 1 liter. The popular mass performs include part of neutroned above. After 1 hours the compared particles by the cotton steps in the reaction. The mystal suspension was filtered. The amounts of reaction components are given in Table 1, heldw.

1 22 3 :

A mixture consisting of D-HFGA (D). (g, 10) mmol, and ϵ -AFA in ϵ (m) water, which was adjusted at a pH value of ϵ . I by adding 4 M ammonium hydroxide, was aide it the reactor with the bottom valve closed. The stirring was started. imministrad Penissilin 3 arylase 2828. Ty size 200-800 .mu.m [made up to 20 rl was a sterior the reactor. The pH value was raintained at 6.1. The reaction temperature was about it is express. The pH value was raintained at 6.1. The reaction temperature was about it. Heaven in These conditions the reaction temperature was as at a settlers, in their first clinicalities for resource must be assumed as a settlers at a settler with 1-HF HA and <u>1-AiA</u>. Then the settler value was applied all with the reaction sixture to settler the tentral declineration, the solution liquid true the central decline was passed into the feet tank wherein 1-HF HA and specific and <u>1-AiA</u> and specific such settlers at as as a settler and as a settler at as a settler at a orn mentrarion of reaction components in the reactor, in the reactor outlet, in the centrofose option, in the impoint and, and in the feed tank outlet were s mitored by analytical HFLO.

The crystals firmer in the reactor were separated from the immubilited engine particles by the bottom sieve in the reactor. The crystal suspension was led to the centrifuge where the crystals were separated from the mother liquor. The mother liquor was passed through the feed tank. When the total concentrations in the feed tank came down to about 180 mM HPGA and 225 mM C-APA, more solid was added to the feed tank. At intervals the crystals in the Sartrifuge were washed with water, the washing liquid was added to the reactor. The amount of water used was sufficient to keep the volume in the reactor at its starting level. After washing the crystals in the centrifuge, the remusifuge was emptied.

[F. F. B. :

After about 12 hours, the desing of $\frac{d-AFA}{d}$ to the feed tank was stopped while the D-HFGA desing was maintained in order to keep D-HFGA at saturation. After 14 hours, the $6-{
m ASA}$ concentration reached 20 mM and the reaction was stopped. The amounts of reaction components are given in Table 3, below.

1881:

1 2 1 1 :

HTLD Analysis of Ampunillin and Dephalexin

Ensymatic Preparation of Amoxicillin from C-HPSM and $\frac{n-APA}{n}$

Shows at its Proper at its of Analysistic from C-HPSA and 1-ARA

Retention times in minutes: 1.9 D-p-hydroxyphenylalysine ; 7.5 D-HFWM ; 3.1 D-HESAN: 3.4 <u>(-ALA</u>): 4.3 Amemicillib).

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Based on the above results, the

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and the form of the sum of the first of the contract of the co	e mm:: 1380 mm::1 67484 443g :.1
CLER: 14. The process according to claim 1, we selected from the group consisting of g T-amino-desacetomycephalosporanic acid, T-amino-3-chloro-3-tephem-4-carbomylate	wherein the amino .ketalastam is T-aminopenisillanis as:i, . T-aminopephalosporanis asid, e and T-amino-3-3-sephem-4-sarbomylate.
OLFA: 18. The process according to claim 1, of from the group consisting of an activa- y-hydromyphenylglycine, D-2,5-dihydrop!	wherein the acylating agent is selected ted form of D <u>phenylglycine,</u> Dhenylglycine and mandelic acid.
CLFR: 16. The process according claim 1, who selected from the group consisting of cephalexin, cephadroxil, cephradine, e	ama isiliin, amoxiciliin, celasior,

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Feb. 1, 1235

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CHAMENT-WERE: 144611 MURYBIOHT 1010 CHRMENT INFORMATION LTD

TITLE: Recovery of C-phenyl-glycine amilia from antibiotic coupling - by tormation of pure, easily sepd. recyclable Schiff base, used in <u>encymatic</u> prepare of cephalemin, cefactor, ampicillin, etc.

COMPANY B: B EXTENT W H T; M TY, H M ; M TY, H

PATENTARIOTORES:

ASSIGNEE ISM NV

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FRIORITY-DATA:

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July 19, 1993

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BE 1007296 A3	May 9, 1995	Ţ.	000	C12P000/00
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INT-CL (IPC): 0070 231/20; 012P 0/00; 012F 17/10; 012P 38/04; 012P 30/04

ABSTRACTED-FUB-NO: EP 712443B BASIC-ABSTRACT:

Frephist a becaming derive is plained in which a beta-lactam nucleus is a pled to 1-premy anyther amide in an endymatic reaction, and the encyme, a literation, the ortion, and therefore which at least the encyme and solid 1-premylacycle have been removed), is treated with an aldehyde at a pH of 7.2-b.1 and the Schiff base of 1-premylacycle amide is sepd. Out.

USE - The occupling reaction is used for prepriof important antibiotics, including ampicillin, dephalemin and detactor, in which the beta-lactom nuclei are respectively of a contecnicillania action e-APA, Teamined esacetom year participation of the APA, and Teamined escape to mederation mylator, and teamined page.

AnyAnyAdE - The 1-thenylglyrine amide deriv is easily sepd. Out in pure form, pref before the beta-lastam prod as the solubility of the latter is higher; recovery and purifien of this prod by known methods, is simplified. Recovery and recycle of the T-phenylylycine amide deriv is by simple filtration or even, in partic of the aliebyde behaldebyde is used, excess aldebyde can serve as extra solvent, although other solvents, or mixts with PhOHO, can be used. The Schiff lase is then split with acid, e.g. HiC.4, and recycled. As an excess of anothers is used in the trupling to obtain a high yield of beta-last and process of anothers is seen as necessary in order to provide a dimmercially action of provide a dimmercially action of provide and in the exception mixt typically contains 1-7 moles of the property of the exception of the production of the process of the proc

m - H - K4, TA Elmova: FMT=APOTRA MO:

Implication of the last amodernia, is claimed in which a best a clast amonutleus is complete to a complete property of the interpolation of the interpolatio

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CONMENSALIBRIES: NO BRRABBE A IIIII: Fem. Hillin and Aphalisgorin intermediates

AH-1:

If the Eppenistic linear acceptable sporting interreductes, for the synthesis of $\sqrt{-444}$, xHamini Hepmen (1985) unus (1997) lying i rmatiin (1994) u (1997) phisphite amid tempound and the conversion of such compound to a desired κ -AFA or "-aminopephem bempound.

B.1112:

Numerous methods for the synthesis of penicillins or dephalosporins have been is suited in the literature. The major part of these syntheses involves the reaction of $\frac{1}{2}$ -amin pencollianic acts in the following referred to as $\frac{1}{2}$ -AFAC, seles and esters thereof or the porresponding T-aminocephen compounds with an activated derivative of the acid, with which the amino group is to be arylated.

In one aspect of the invention there is provided a novel intermediate for the synthesis of derivatives of 6-APA or 7-aminocephem compounds in high yields.

The structure of the congruends having a route 1 has been established in the course of their 15 and 1998 spectra \times 1990, The spin-spin oruging pattern of the latter shows that the calpha. Haydrogen of the C-aminorephen derivative is strongly unfluenced by the introduction of the phosphorous atom.

In eqAPA derivatives with a free NH.sub.2 -group the proton in the e-p sition is namedly seen as a doublet at .delta.v4.4 - 4.0 ppm - TOLLsub.8. However, as an example in a p-APA temporal having the formula 1, of. Frample 1, this proton is found as a multiplet consisting of a peaks in the region of .aelta.v4.0 - 1.0 ppm - TOLLsub.8, iron which by first order analysis the rollowing adir sibate organis constants can be ditable in

It is even more surprising that a compound having the formula I, wherein R is a secondary ammonium group can be reacted with a halophosphite compound to form the corresponding phosphiteamide compound. However, it has been found that for example a main penintiliance and or T-aminodesa estawy explains paramonally, when the presence of two modes of the presence of two modes of the thylarine reasons with the example estaylene children phosphotosis as to firm a main was a tree another phosphotosis. to form on main was a the abethylar conversalt of estimating high split card or

7-orthyloneph.seph.room.nomesa.estoxyoophalosporanio armi and disthylammonium chiralis. It might have been experted that ethylene chiralphosphite would sear exclusively with the excessive mole of secondary anche.

No eminate a armin which in the propagation of penincillin and regular apprincipations from <u>Famin Finitellance armin</u> Teaming reguence is approximation of the result and the mail is the quently used in the presente of a

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The control of the second control of the second projects of the second s period the expessive alkyl amine but, in the other hand, a hydrihalide a meghor is he massary to grimote the resolution.

The Control of the American period of the American section Section of the American Section Sec entryleneph spinitearch or regular to the responsibility of smultake daily the extessive and in the amine continuent of the extessive and in the continuent of the symmetry of the symmetry, at this stage of the symmetry, I make it trialkylsilylhalide, I make of extrylene while representation of mode of a reactive alkyl halide may be added to form the corresponding ester.

Among other activated acid derivatives which have been used in the acylatics. of the amino wroup of $\epsilon_{
m CAFA}$ or derivatives thereof are various forms of aminared esters, e. r. rentrophenyl, symmethyl esters and the like.

BOFF:

Few syncheses of genicillin or cophalograph derivatives are known in Which a free carboxylic acid is reacted with a derivative of 6-APA or a 7-aminocephem hompound.

The specification of British Patent No. 1.268.836 discloses that 6-isobyanato positivitative and is may be prepared by reacting phospete with a $\frac{c-APA}{c}$ esfert The (-isocyanato penisillahis ester may then be reacted with a free acid to yield a penisillin derivation. However, this reaction can only be performed with miderate yield, and furthermore this known synthesis is not fully arreptable because of the use of phosgene which is poisonous and technically alizionlo no handle.

BRER:

The above reaction can be illustrated by the following reaction scheme, in which a 6-MPA derivative of the formula I is reacted with a carboxylic acid: ##STRo## in which R has the meaning defined above, and R.sup.3 is an organic mour.

F::F5:

In a purpley embodiment of the method of the invention phthalide esters of seniellin and equal sprin can be prepared in high gields from +=anthopeditorileation and the =amino explore acids without effecting and
epimeric without 0.sub.# or at 0.sub.T..

BSER:

Fig. 15 millimoles of ϵ -aminopenicullation acid whAFA are dissolved in 19.5 ml associative by addition of 0.5 ml (2) millimoles of tricthylamine, and the colors of the posterior of 40, kepter 7. To this solution is added in and he could be seen that the court of the providence of the second of the court of

The x is millimoles) of x-aminoperiodilario and are dissolved in 10 ml of dilutoform by addition of the x-and 1.50 millimoles) of triethylarine. The solution is solved to -10.8 green. Sand 1.57 x [1] millimoles[10] are tryloul to proceed to a side is in pwise under dry nitroder. The mixture is

starred consistency ± 1 , we green it and in then negleck to the motorper at its and

Try enner is added to the mixture to presipitate the triethylanminium chlorise turnes. The salt is followed orf. The filtrate is evaporated to a white war which is very hygrisospic. The product is stable in fold, dry solution and when stored under dry hitrogen. The product may contain small amounts of unreacted <u>standageneous lands agod,</u> troethylamminium sait.

E-12E:

1.1. a temilim les of <u>e-miniper. til and a til</u> are dissolved in e-mi Thoras for any the latter in the 1.4 millimites of triethylanine. The Thoras for the court (e-complete, temperature) stirring of millimites or departuylete hit moet, solo dissent with a disserted in a mit unitraform are assess under dry not deni stirring is continued for it minutes at eblomesters. Then subsequently to the number of the temperature. If no dry benden are added. The trietny ammentum shieride pormer is separated by filtration. Turing said filtration part of the product is lost, but the filtration is normally unnecessary when the product is to be used for further reactions.

1. For a condition was of <u>e-aminopenitionally avid</u> are dissolved in 8 ml dry aretonitrile by the admittion of 1.40 ml dismillimoles of triethylamine while stirring. [.45 ml d millimoles] of 2-phloro-1,3,2-thiadxaphospholan in 2 ml dry abetonitrile are added dropwise under dry nicrogen and at a temperature of about -40.degree. C. Subsequently the solution is stirred for about 1 hour at room temperature.

1.03 ml (10 millimoles) of diethylamine are added to 1.08 q (5 millimoles) of v-amingrani dillani dadisi suspended in 10 ml dry abetonitrile. After stirring in a mitropon armosphere for 2 minutes, a clear solution is obtained.

BOHB:

The assignment of 1.1% got millimoles of $\frac{1}{2}$ -APA in 10 ml of dry methylene chloride are added 1.4 ml old millimoles of triethylamine, and the mixture is stirred at room temperature until a clear solution is formed. The solution is Scoled to -40.degree. 0, and 0.46 ml (6 millimoles) of ethylenechlorophosphite Hissalvel in 3 ml of dry methylenechloride is added under dry nitrogen. The mixture is stirred for 11 minutes at -40.degree. 7, 15 minutes at 0.degree. and 15 minutes at 100m temperature, thereafter 1.60 ml (5.3 millimoles) of trimethylohlorosilane dissolved in Comblor methylenechloride is added. The rigidure is stirred for 3 minutes at room temperature, and subsequently the precipitated tristoplanous hydrochloride is follored bif. The solution is braphiated to form a hard, pale yellow bil-

l g of <u>N-AFR</u> is suspended in 15 ml of dry methylene chloride under nitroden. To this mixture are added 1.40 ml of dry triethylamine and 0.60 ml of Frimethylphlorosilane. Atter stirring for I hour the reaction mixture is socied to -file meet. 2, and a solution of 0.87 ml of -phonylene chi orogic spirite in 5 ml of try methylene shioride is added or phonylene chi orogic spirite in 5 ml of try methylene shioride is added or passe. When the addition is to make the orolling is stopped, the mixture is storred to 14 minutes, and the solvent is removed in value. Try bender, is added, and the tributory are now this rise is removed by filtration when nor ben, the bennene issuer we take the repute to the an inches a few for the estraiphaint as an araphas suistana.

inion a Bu millimoles of Delete.bota.-phonylalycylchloride, Hollare then alled to the reaming marking, and valid mixture is stormed for I hours at In the proof of th en de la companya de la co

the orn believe who more thoroughly washed with water. The orphic thas play opporate cannot be appeared practice which will expect the confidence of the confidence of the capability of the capabil nours while stirring. Stirring is continued for about 1 hours while lowering one temperature to itae meet. To Stank opernight at the effect of The precipitated dephalemine wetalenaphinul ormpless to separate any filtration up: washes with water and putylaretate. The washes pre-tiplinate is a specific in 10 of water and 16 of pulylanetate and the pH is far taken at 1. Joint a LEE taken at 22 is luttion. Sussequently the mixture is filtered and the aqueous phase is washed twice with a milkutylapetate. The pH=value of the aple we phase is amosted at 4.5 with triethylamine and the value of the mixture is reduced under various to 8 min 10 $\,\mathrm{ph}$. 1,1-limeth wyethane are added and the mixture is stirred while being of the CTS to bree. The research about the was. The mixture is left to stand twomight in a retrigerator at fidegree. The prejipitate formed is separated by filtration, washed with water and dried in an existion.

4.33 g (21 millimoles) of D(+)-phenylglycylchloride, hydrochloride are added in particus over a period of 1 minute to a solution in methylene chloride of c. millimoles or trimethyls:lyl-6- ethylenephosphiteamido penidillanate prepared as described in Emample T and without renowing relatively and the following the second of the progress of the reaction is colleged by periodiclinase totration union untor a period of a hours at 1.degree. I shows that a yield of above 70, has been obtained. At this time the reaction mixture is poured into 100 ml ice-water, and after stirring for 15 minutes the reaction mixture is filtered. The water phase is covered by 20 ml ethylacetate and the pH-value of the water phase is adjusted at 2 with a NaOH solution. Subsequently, the ampicillin formed is precipitated as a sparingly soluble salt with .beta.-naphthalenesulphonic acid while maintaining the pH-value at 2. The reaction mixture is left to stand for 12 moved at 1. Fares. Transition subsequently filtered and the residue is washed with puril Holland ethyladetate. After drying in vacuum 7.2 g white amplyillin .beta.-naphthalenesulphonic acid salt corresponding to 64.5 of the theoretical amount are obtained. A high-voltage electrophogram showed one spot with mobility identical to that of authentic <u>ampicillin</u>. The IR spectrum was identical to that of the .beta.-naphthalenesulphonic acid salt of authentic 11.51 11.11.

nerm:

1.10 in 1. millim less of <u>resmit percolliquit and</u> are dissolved in e-ml any alphaletree chlorotom by the addition of 0.8 ml (40 millimoles) of trietlylamine, 1.30 ml (11 millimoles) of trimethylchlorosilan are added impulse and the reaction mixture is stirred for 1 hour at room temperature. As e- .degree. 2.1. Fold to millimoles of ethylene chlorophosphite dissolved in 2 ml dry alocholefree chloroform are added dropwise. The reaction mixture is stirred for 1 hour at 1.degree. 3.

1.16 more this compound of millimoles and 1.10 more provided hydrochloruse are insected in 1.0 millimoles and tylene objects and heated to reflow. A country of confilm less to trip thylarly:
--thyleneph spints arrive middlenate in 1.0 millimore after the addition is absented shows a penicillim yield of 30, while titration after one and two noise both shows fill yield. noirs both shows blo yield.

Barr:

serm.

4 millimoles of N- term.-buroxycarbonyl-D-1-.alpha.-phenyl/jycony
crimothylsllylester prepared from 1.71 a 4 millimoles of
N- term.-buroxycarbonyl-B-1--.alpha.-phenyl/plycony, 10 ml of chlorotorm, 7.17
nl 4 millimoles of triethylamine and 7.61 ml 4 millimoles of
tripethylonic resilance by stirring for 30 minutes are added to a solution of 4

If (x,y), 2. The control of 111.degree. Of for 1s hours. Then the mixture is evaporated in varuum to aryness. The residue is dissolved in methylene chloride and washed twice with dilused hydrothloric acid and twice with a solution of sodium hydrogen ny morni. Ele accidant twice with a solution of sodium hydrogen Park Shate. The ny no omitono no vivo della compositione di compositione della composi ugina. eginenyu suginyilar da ille segihe kemede dassi xydatsa.

EMER:

To a solution of 10 millimoles of trimetnylsilyl- --ethylenephosphiteamiat -penitillanate prepared as destribei in Example % from Life with g = A + A, in dry methylene dilloride are added 1991 ϕ In millimoles of then myaretic acid, and the mixture is stirred at 100m temperature with dry air bubbling through. After a reaction period of a hours at room temperature the reaction mixture shows a peniodilin yield of the by empyration invation. The reaction mixture is choled to 0.degree. 0, and 8 ml of pyrodine are addedically wed by 28 ml of dimethylsulfoxide, whereafter the reaction mixture is poured into 800 ml of ice-cold 10. NaCl solution and the second second cold second to 0.00 ml of other second cold and the period of th stirred for 30 minutes. Then 150 ml of ethylacetate are added and the pH adjusted to 2. After 30 minutes the phases are separated, and the water phase is extracted three times with ethylacetate. 25 ml of water are added to the combined organic phases, and the pH is adjusted to 7 with KOH. The water phase is separated, 150 ml of n-butanol added and the water removed by azeotropic vacuum destillation. The crystalline crude product thus precipitated is filtered off. Yield: 3.16 g (81) of a purity of 76 determined by penicillinase titration. The white, prystalline product shows a characteristic absorption in the IR spectrum corresponding to that of the potassium salt of pheno wymerhylpenicillin, and the MMB spectrum also shows signals which are Shara Heristin di sali ompound.

H-3774:

.61 a 4 millimoles of phenomyabetic acid is added to a solution of 1,2,00-trichloroethyl-S-methyl-Tubetal-Jethylenephosphiteamido - seth-s-e m-4-carboxylate in abetonitrile prepared as described in Example 11, except for the differences to remove the precipitate of trietnylammonium chloride. The mixture is stirred for 1: hours at room temperature. The reaction mixture is then purpose into instructor and extracted three times with ethylaretate. The Springs of this these are washed three times with 2 M sulfurio acid and three times with saturated sodium hydrogen carbonate solution, dried over Mass.sub.4 and evaporated in vacuum to form an amorphous powder:

4.76 g of N-parhobendoxy+0 -1-phenylylycine in dry methylene chloride at from temperature are added to the product (6.5 g of benzyl R-ethylenephosphiteamidopenicillanate) of the roduction described in Example A under nutrigen. The mixture is stirred for 4 hours, evaporated to dryness, tion in definition of a synthyla per abound on them with loo-water of wice , The contract of the contract er een brondigt die voor

H.H.H.:

1.v1 g (4 millimoles of N-)tert-butowyparbonyl -D(-)-.alpha.-<u>thenyl flyothe</u> are added to a solution of

pty. typt-repart or or hylese report by LeT. beta. elet by Lenephosphite amidal e pephese e The second control of of the control of the

phases are washed three times with a Wi<u>rachel tipus</u> and three times with a storate room of an area of the control of the con

Form. The proof $\frac{1}{2}$ and $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ are dissilved in TD., and of a setunity ile by addition of $\frac{1}{2}$ $\frac{1}{2}$. The proof is solded to $\frac{1}{2}$ \frac the temperature in a cally barses to be respective, the triethy and object militare in the way first stade.

A solution of the oriethylammonium salt of Geshylene phosphite amidopenisillanis asid was prepared from 2.16 g (1) millimoles, of ℓ -aminopenisillanis asid in the manner described in Emanyle 1 and the triethylammonium shloride formed was removed by filtration.

The MMR spectrum ($^{
m ML}$ sub.3 CM) of a sample of the reaction solution showed that all <u>e-apling-publicance sold</u> had been converted into the corresponding emplete ph sphileshid our sund, and the following characteristic signals were trialned:

has the meaning defined above with a salt of $\frac{e-AFA}{e}$ or of T-aminocephem acid or a derivative of said acids.

The coupling constants J.sub.P-N-O-H, J.sub.H-N-O-H and J.sub.H-C-C-H are ounsistent with three frunk in literature (for F-M-CH.sub.3 compounds are normally found J.suk.P-H + 8.8 - 25 Hz (Japkman and Sternhell: Applications of Musigar Mashetts Residence Spectroscopy in Organic Chemistry, vol. 5, p. 352 [1989]. The coupling J.sub.H-C-C-H = 4.5 Hb is also found in the simmal doublet from the proton in the 5-position in ℓ -APA. This pattern in confunction with the signal of the 3-hydrogen and the infrared absorption rrequencies of the carbonyl group in the 3-position which are consistent with those normally found in $\frac{d-AFA}{d}$ derivatives, is a conclusive proof for the presence of the structural element: ##8TR5##

Generate Collection

8110:111

COMENTALSENCIPIES: US 4:1:11: A TITLE: Propose for greparing dephalosporation and dompounds

B. 11 B :

The content of the cutters are to prepare percentaged in the arm and regress spin range and serious are substituted by a quanting $\frac{1}{2} - \frac{1}{2} \frac{1}{2} \frac{1}{2}$ or $\frac{1}{2} - \frac{1}{2} \frac{1}{2} \frac{1}{2}$. A and their derivatives with the hydrochloride of $\frac{1}{2} - \frac{1}{2} \frac{$ optained by reacting the substituted phenylglycine with reagents like phosphorus pentachloride, thionyl chloride and phospene. Although improved processes for the preparation of $D_{\tau}(-)$ -2-(p-hydroxyphenyl)-glycyl-chloride hydrochloride and the crystalline hemidicxane solvate thereof are known from 8^{2} : tick Part. No. 1,466,637 and No. 1,460,918 the adylation of 6^{-} AEA or NHAIDICA or its 3-methyl modification with the above-mentioned acylating agent did not hitherto lead to results aimed at, mainly because either the product formed was too impure that further recovery of a product of the required quality hardly appeared to be possible, or the starting d-1- p-hygroxyphehyl -glycyl chloride hydrochloride of the required quality (purify) is only available for economically unattractive prices, if at all.

HREE:

A process for the preparation of amoviouslintrihydrate is also known from published German patent application DT 2611286 comprising the anylation of -APA, which has been previously silvlated, with THE THEFthy in many heavy of the same extent the present practical requirements.

HOFFE:

However, in the preparation of $D=\{-1,-1\}$ p-hydroxyphenyl)-glysyl diloride hydrochloride according to the British Fat. No. 1,460,815 and British Fat. No. 1,466,637, phosdens is used in a relatively difficultly manageable process in which a solid is reacted with a gas. Such a process is extremely expensive in a number of countries with very stringent safety regulations, if indeed it may be applied at all. For the same reason, the process described in British Pat. Los. 1,0ex,0ex and 1,341,500 disclosing the proparation of weisogramatopenicillanic acid and T-isogramatopenicillanic acid and T-isogramatopenic acid derivatives from esters of 6-ADA or 0-ADA or its 3-methyl modifications with phospene and the advergence from the first period of the property of the first or one period line or openal stories are left of the content of the first period Singular and in the congression of the model and the dephalosphrants and period the scaling the correspondent size of aim in Figure 1 in.

less attractive reatures or this process are that the process is carried out The second section of the second seco

Furthern re, a number of papers applications and patents disclose preparation perhods of Lalphal-aminoabyl-penibiliance acid derivatives by applating <u>stata</u> with mixed anhydrides derived from modified Tane salts of T-2-amino- p-hydrowyphenl -acetic acid, such as those described in German

parent Applications Ser. H., 1, to , talk, H. ..., 19th and H. ..., expects and Hellish Harden Hard purpose if the present invention, and mare ver, the lane saits eppeared to be avaluarle un efinimically distributive grantities, li at all available.

And the state of thereof should, in a number of bases, lead to improved yields, as appears, such as from British pat. No. 1,266,549 displosing the preparation of intermediate organisilane penicillins by reaction of $(4-\lambda FA)$ and those Ri-functional silicon compounds. The organosilane derivatives are ac into ampicallin for example, so that an empert from the contents of this parent would expend that the use of the ordanisilane penicillins described there in would lead to interesting yields in the preparation of animal collinations. most war, this expectation of hit suprishing not be confirmed by initial errent en trent de

Although it is further known from a number of patent applications such as Japanese Patent application No. 49-114687 and No. 49-048892, British patents No. 1,367,342 and No. 1,362,255 and German patent applications Ser. No. 2,462,649 and No. 2,621,619, to prepare amosticilis. from C ANA and p-hydroxy-phenyiglysine or lower alkyl esters thereof by ensymatic acylation, the propesses of tils type are also unsatisfactory for the deemed purpose in view of the yields ortained and or the presence of the applating encycle in the anomibilin-pontaining solution obtained.

It has been found that the way in which the silylation is carried out is very important for the final yield, and the silvlation is preferably carried out in dry methylene chloride containing 2 to 3 equivalents of a tertiary amine such as triethylamine and an equivalent amount of TMCS (about 2 equivalents for amomibillin and perairomil and 3 equivalents for befatricine, in such a way that the similiter idea by a pH electrode is adjusted at the end of the resultion at a constant value of, for example a pH socie value between b. F and cannot be a beginned on pH meter type TTTL, 0 and a the, greater day to Radiometer NK 14 to Wikewicke or an Ingola, so-called cold electrode, at a temperature between 10.degree. and 10.degree. C. Therefore, disilylation of e.g. of e-AFA or "A.D'CA is preferably carried out with practically balanced nutual amounts of trillower alkyl' halosilane, such as TMCS, and tertiary amine (such as TEA).

The raint to a further presented process, the solution of the annumble as prepared to the annumble as prepared to the solution of the annumble as prepared to the course of the course o second of the control . to 430.degree. C. is reached, whereafter the reaction mixture is stirred for a purcher 0.5 to 8 hours. An excess of the formula V compound is response to the distribution of the compound of formula U will be necessary.

thospill as appropriate bornar some of the most important advantages of the any, and high coses of the Consention area previous and selective splightion of a particle processor of the control of the particles and stand can be expected by the property of any order of the average and the property of the expected by the competitive and the expected by the expected of the expecte will favorably incluence the output in biles per batth; the use of a

9 1 00 2:44 PM 2 of 6

property by a rather will thity menages in process and which is the verilable property by a rather will thity menages in process and which is the verilable extremely expensive in a number of countries are to very stringent safety regulations, in indeed permission for the manufactories and reconstruction at all, the use of caree as untsold their additional onemitals is avoided; the desired final property can supprish ply be prepared in estimately attractive initial yields on a partity attention under available nearth regulations while at the area time, the number of partitions to prove an accretion of a ovent of the that her very its observable as a rather supple and estimately advantage of and or very the starting of the power of arther supple and estably easily interpretation of an account rather than the second of indeed and make the process of an account respective of that is a reconstruction of the process of an account respective of the process of

B. 1 B :

the application of the convent systems for indicate preparation of the mixed stay more comprised by appears to be and the mixed and unit vertains for the mixed and unit vertains for the mixed and unit of the animal proves yield of the desired of my cunit, in an improved yield of the desired of my cunit in a maintain, with a simultaneous in mease of the concentrations to an attractive level, with reference to the presented nomical requirements; is, the rather unexpected application of N, estimated and TeACA or derivatives thereof for the reaction with the mixed anhydrides in the indicated yields; (d) to improve conversion vields in the case of the application of the application vields in the case of silvlated TeACA derivatives; and each the possibility to carry or the silvlation reaction and the preparation of the mixed anhydride in one and the wave water imprisible main solvent, and note particularly of converts in maximally singlified.

BSIR:

As in industrial provesses the application of the roughly dried solvents and/or lane salts of very high purity is an ideal that will never be realized completely, a slight express of the starting lane salts and of lower alky, on, a formates are preferably used. In the off-the preferred end diments of the pressure of the presented invention, as middling troughly to prepared, starting the only being seen to the presented in the presented of the presented in the presented of the editation with respect to a present and in an amount of about two equivalents with reference to applicate with N-methylmorpholine as canalyst, and a cosolvent selected from N,N-dimensional mode, N-methylpyrrolidane, N,N-dimensional properties and tetramethylurea or mixtures thereof, and methyl chloroformate, while the solutions of the in situ prepared silylated m-AFA abid and the niwel analytic at prepared solutions of the in situ prepared silylated m-AFA abid and the niwel analytic at prepared solutions of the instrument. As a meet. The above the solution are xibillingly known methyles.

ENTY:

in $\frac{1}{2} \frac{-ATA}{A}$ is a neglective with an embession astronometricity animal base such as triefly lamine in an inert, water-incolable manifest livent such as neglected with ride or unlimitable resulting in a solution of a stalt of $\frac{1}{2} \frac{-ATA}{A}$ with the rate on said solvent,

1919:

A control of a control of the contro

3 of 6 9 1 00 2 44 PM

of the starting HESO appeared to be result as almonia.

The first percentage of the property of the were well their first and the action between and or only of methylene of their experience of the restriction of the true were after the reperture and the non-first property of the true were after the reperture and the non-first property of the result o

: EFF:

In a nitrigen atm sphere, first p=40 mm less of r=A1A were suspended in the right probabilities will be madiled out triethylamine and the right modes of triethylamine and the right modes of triethylamine partane were also example pently. This mixture was refuseer with stirring tor 1 nour and then was to lead in an loss path to

With vir rous stirring the turblid solution of the Cane anhydride prepared in Step A and to left -0.1 degree. A was affected all at the total collection of the silvlated $\frac{1-A+A}{1}$ obtained in Step B and the mixture was stirred for a turings of minutes in a life bath. Then, the life bath was removed but stirring was continued with intriduction of hitrogen until room temperature was reached shout 40 minutes . The minture was poured into with rooling 75 ml of ice water, whereafter the pH, which reached a value of 2.8 to 3^{7} was addusted to 1 to 1... with a naventrated hydrochloria acid as measured with an Electrofact KCL electrole in this to 0.7 with an AgO1 electrone.

In substantially the same manner as described in Example ε_{ℓ} amost dilling tringdrate was litained in a yield of Tiles with a med surmetrically measured purify or 48.8, a biologically reasured quality of 96 and an optical rotation [lalpha.].sub.lo.sup.D of +350.degree., starting from 42.5 mmoles of potassium D-laipha.-Ti-parboethoxypropen-2-yi)-amino-p-hydroxyphenylabetute in Termio forethylis borylketone and Bormio foretrahydrofuran, 2.25 milof Merothylm sphiling, 44 mothes of terrachlor formate in 18 ml of Both p Hill bubyled the Add and leed to e 2 程度 in 13 call of proportioned at the A op troothylands and so ED less to tripethyl milyr silane.

1949:

In substantially the same manner as bearified in Example -, amoximillin tribyinate was ibtained in a yield or the having a purity of ME according to hydroxylamine measurement, a biologically measured quality of M4.4 and an $\operatorname{cgt}(\operatorname{rat}(x))$ at $\operatorname{cg}(x)$, $\operatorname{sub}(\mathbb{R}^n,\operatorname{sub}(\mathbb{R}^n))$ of $\operatorname{red}(\mathbb{R}^n)$ by $\operatorname{red}(x)$ starting true $\operatorname{Af}(x)$ rm fles of potassium

.a.g.na.- .- rank meth wygi gene.-yl -amini-genyaniwyyhenyla metate in 94 ml etrylia alitylaet segara et milototeti nyan iman, . . O mlot Merchnylm spin line, 40, kom les in metnyl sil het mate i puniture in 10 m of metnylis motylis me, 4 mulles of <u>resek</u> in 15 millionstry methylene omloride, - 10 mm les of triethylamine and of mm les of trimstrylchlor sil des The (E value measure) with a Hadiometer (E meter TIT L, C and a Fail meter & Note that was kept a distant at 0.4 at the end of the solylation marin.

The children's alloyeth covaries maintened as described in Emarque (*) am misplito The chart and alloy the charte manners as described in Françis by an windling throughout the control of the charter of the cha

 $r = \frac{1}{2} \frac{1}{2}$ For The less intrincting the resiliance. The pH trained measured with a said not or pH notes type TTTL. Thank a Said meter SE 24117 electrical was adjusted at 2.7 and the endirective silvication reaction.

n statistically the sere parker as described in Exemple e, amomibilizing Was disched in a great of a newtrig a permit refer inally peasure:

The state of the s M-metrylmospholine, 44 mmoles of ethyl chloroformate in 30 ml of metryl is butylketine, 40 mm; les if <u>6-ALA</u> in let mi of dry methylene shliride, 6..e mm les of trietnylamine and 62 mm; les of trimethylahlirosilane.

 $[-1] + \frac{1}{2} \frac{1}{$ This of methylene filtriae were saded thereto. After addition of They or pis trimethylsilyl -urea, the mixture was refluxed for about 2.8 hours and the mixture was then cooled to 20.degree. C. The "pH" reading, on the scale of a Radiometer pH meter type TTT 20, connected with a Radiometer GK-24010 electrode, was 6.3.

DEPR:

In the same manner as described in Emample 13, 49.3 g of amoxicillin trihydrate having a purity of 97.7% were obtained by reaction of methology rank troy!

I-.alpha.-'I-parkomethowypropen-2-yl/-amino-p-hydrowyphenylacetate and 38 g of y-amingpenialliania army previously silvlated with 72.5 g of bis trimethylsilyl, acetamine instead of the bis trimethylsilylyurea.

DEPR:

En Silylation of <u>E-ABA</u>

to that t =AiA decay is feater 4 of plant methylene unformide. After addition of 43 no di tristipo anche at amicent temperature and under stirring, se mi cr trimethy. Enlarged are aried in about 1 minutes at a temperature of 10 degree. - If degrees. 2. After additional stirring for 1 hour the "pH" value is adjusted to a final value of 6.7 by the addition of 4.9 ml of rimethylohlorosilan. The mixture is cooled to +40.degree. C.

In the same manner as described in Examples 13-15, 55.3 g of amoxicillin Tribydrate are obtained in a yield of 41.5 having a purity of 99.9 assording to a try by more metros resemblest, a biologically peagure approximation of 30 co menomeratrically be assisted purity of Gale , and an optical retainen ...elyha.).sub...).sup.D of +90, stanting from 05 % of potassium The sign of the configuration The "pH" value measured with a Badi meter pH meter TTTL', and a Badicmeter TK $24 \cdot 15$ electrons was adjusted at e.7 at the end of the silplation reaction, while the solution of the mixed anhydrode as well as the solution of silplated $e = \frac{24.8}{100}$ were both previously to be to = 4, degree. The and reacted at = 81, degree. Note that the state of a plant on piele (4.1)

In the same pather as assimilation Examples In-In, As.I more as wisilling triby hate are ditained in a yield of El. To having a purity of Re. To asserting to a hyproxylamine method measurement, a biologically measured purity of $\Re r$, a mercurometrically measured purity of your and an optical resultion (.alpha.).sub.cl.sup.7 or +300, starting from 56 g of potassium

In alpha to letter meth wypropendacy confine peny may beny laws are in a confine methylene multiple and a confine of the perhyl microproate, which is $\frac{1}{2}$ -ABA in all of an ethyl microproate, which is $\frac{1}{2}$ -ABA in all of a confine throughout the perhyl makes and as former triple himself and a former perhyl himself and a substant as $\frac{1}{2}$ -10 electropic was appared at $\frac{1}{2}$ -10 at the end of the silylation reaction, while the solutions of the prime and the silylater $\frac{1}{2}$ -AiA were presented at $\frac{1}{2}$ -10 and reacted at $\frac{1}{2}$ -10 and $\frac{1}{2}$ -11 and $\frac{1}{2}$ -12 and $\frac{1}{2}$ -13 and $\frac{1}{2}$ -14 and $\frac{1}{2}$ -15 and $\frac{1}{2}$ -15 and $\frac{1}{2}$ -15 and $\frac{1}{2}$ -15 and $\frac{1}{2}$ -16 and $\frac{1}{2}$ -16 and $\frac{1}{2}$ -17 and $\frac{1}{2}$ -17 and $\frac{1}{2}$ -18 and $\frac{1}{2}$ -19 and $\frac{1}{2}$ -19 and $\frac{1}{2}$ -19 and $\frac{1}{2}$ -10 and $\frac{1$

1515:

In the same manner as described in examples 13-15, amovicillin was prepared in a 51 acylation yield starting from 55.1 g of potassium. Detalphate 1-parkimethologypropen-2-yl -amino-p-hydroxyphenylapetate in 471 ml i methylen-onlinide, λ onligi N,N-dimethylformanide 1.5 ml if N-methylonoriph time, less interphylonority materials, λ of λ of the first methylonority of the first potasion of the first methylonority of the silvane. The "H" of the reasoned with the same equipment as in the pre-section examples was accusted at λ of the end of the silvation reasoned, while silutions of the mixed annualized and it silvlates λ -AiA were pre-scaled to -41.degree. C. and reacted at -51.degree. C. for λ hours.

DEFU:

STEP B: Silylation of V-AFA

TEFT:

STEP B: Silviation of F-AFA

DEPU:

STEP B: Silylation of 6-ABA

WEST

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40.04: 11.14.1

B.11 H:

Anylation of the description of up of a tephanispoint, for example, of each original context of the teaming group of a periodic resolution of the teaming group of a periodic for indication of the team of the team of a compound of a context of the team of the team of a primary and of the context of the tree and are known. The tree and can be upled with a compound of Fernila III or with the original resulty-cleavable extens, for example, in the presence of an encymptor of an N.N'-carbinyldimidable or of an N.N'-carbonyldiff and the context of the context of the carbonyldimide of N.N'-disopropyl carbodimide, N.N'-disyclohemyl carbodimide or N-cyclohemyl-N'- $\sqrt{2}$ -morpholimoethyl,-carbodimide.

H. 11 H :

ther iseable and varies derivatives or close the corresponding an lines, i.e., and we do corresponding a class, the amide nitroden of which is a merieon of a quasiaromatic temporalised ring which contains at least two nitroden atoms, for example, or an imitable, pyrabole, triabele, benchmidable or behond riable ring. Another useable derivative of a substituted theorylylycine of Formula [IIII] is a N-parboxyanhydride (Leuchs' anhydride). The group which activates the parboxyl group here also protects the amino group.

B. 11 B. :

For example, 7-A World terminal Toward of the FAIA terminative esternian be reacted with a regular of Formula Toward FAIA wherein Formula is apported in a morphism to take a specific and FAIA and there as an very with a hydrolytic of my more light terminal and with 177 in substantially equivalent proportions, with a limit, in an insert of Event, expectably in a chloridated hydrodam in, of more methylene chloridate, in an ether, such as THF; or in an appoint dipolar is Event, such as EMF or EMSO; or in a solvent mixture.

$u_1 \cap u_2$

From the first or point which of the rwise corresponds to Ferrula II, but in which Foreign for an Aussia +-100, in μ , $+-\mu$, μ , with an alkylating a but usually take place in the presence of an ability tatalyst, pretending to a summariant μ , μ

The inflowing additional are used in the Examples: IMF dimethylformaniae, IHA Wall-amin rephal sporuhic acid, <a href="https://www.normania.com/real-Aminopeniallania.com/real-aminopeniallania.com/real-aminopeniallania.com/real-aminopenial-aminopeniallania.com/real-aminopenial-aminopenial-aminopenial.com/real-aminopenial-aminopenial-aminopenial-aminopenial.com/real-aminopenial-aminopenial-aminopenial.com/real-aminopenial-aminopenial.com/real-aminopenial-aminopenial.com/real-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopenial-aminopen

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Indicar as not observe estates, substituted . His englishing of Formula III, or the period times there is also in the formula Formula III are then because as mixtures of two

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Fig. 11111

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Adrille :

A project to the first term of the experience of the first to the first terms. catalyzed acylatics of the parest sheta. -lactan with an activate i derivative or the side dhain acid wherein a modulator, which consists of one or more compounds different from the reactants and the reaction product and which suppresses the hydrolysis of the activated derivative of the side chain acid and the desired product more than it suppresses the synthesis of the desired product, is added to the reaction mixture, at the heginning of the reaction process, in a concentration from about 1.2 to 101.times.10.sup.3 .mu.m.

E388:

The present invention relates to an improved method for enzymatic adylation. in particular, the invention relates to the preparation of .beta.-lactam antibictics by enzymatic adulation of the parent amino .beta.-lactam moiety with an applicating agent which is an activated derivative of the side chain asid.

BSPR:

Entrymentia production of semisynthetic operatelastam annihistics by acylotics the parent amino .beta.-lastam milety with the side chain acid or an aminutes bringsing, sum as an amile or an ester thereof, is known e.g. from West Berman patent application having publication No. 1,163,79., Austrian Fatent No. 143,980, Dutch patent application No. 03-04138, West Berman patent application having publication Mo. ., 6.1, 615, European patent application having publication Mo. 388, 781, international patent application having publication Mo. 388, 781, international patent application having publication Mo. We shoulded and from international patent application having publication No. Wo 43/12251.

ESER:

PSFR: The parent amino .beta.-lastams such as $\frac{6-\text{aminopenicillanic acid}}{6-\text{aminopenicillanic acid}}$ and The parent amino .beta.-lastams such as $\frac{6-\text{aminopenicillanic acid}}{6-\text{aminopenicillanic acid}}$ are commonly produced by ANY LICENSES OF A Following Spinistilly for every a periodillin V and the learner ation, the the subtraction of the second of the subtraction of 10 -10 bm. The work solution can be purified and orystallines to prain pure than or that the continuous to property or the continuous to property of the continuous to property. Through a rearrangement process before the hydrolysis step).

A mawhark of the Anown methods its <u>graymatic</u> production of theta. Hartam and the total of the particular arise that all the particular arise that all the particular arises. a remark to the first of the main a trib is that maker the dearth is conditions used part of the way, a interprise hydrolyses before it has beautel with the amin lestal-last et. Thus, when the abide of the side chain acid is used as the first agent, some tree side chain avid and an equivalent amount of amounts ϵ will be generated in the reaction biwture as a result of this hydrolysis. Dimilarly, when an ester of the side chain acid is used as acylating agent, some free side chain acid and an equivalent amount of the alcohol corresponding to the ester will be generated in the reaction mixture as a

result of the hypolysis. Also, the desired project formed hypolyses to form tree wise chain as a and the parent amin our tax-cast at.

to the new, sumpressingly, week from a that resident modulations, i.e. complement To has new, sumpressingly, week from a that resident modulations, i.e. complements accidental into the ise mants and the iseastion product, can be added to a B 1 B 2 when it is considered and seek and respectively about 1000, in 2004 and 1000 an That the dyst lysis of the applatiful apend-some an artiface beginning to the state chain and is used as abplicitly agent-rand in the desired product is suppressed mure than the synthesis of the desired product.

rund.
Associatingly, in the highlest aspect the present invention relates to a method aspectingly, in the highlest aspect the present invention by enginetic asplation of providing a second provide the side of air and a stock the present of the side of air and whether a provide to which suppresses the hydrolysis of the adjusting and whether a provide the suppresses the hydrolysis of the adjusting and whether a provide the suppresses the hydrolysis of the suppresses the suppresses the suppresses to suppress the suppresses the s the analysis of the specific problem of the supplementation of the synthesis of the desired product is added to or present in the reaction mixture.

Examples of .beta.-lastam antibiotics which can be produced by the process of this invention are amprocillin, amomipillin, tiparpillin, pefacior, Defatrizing, pefarato, pephradine, pechalexin, pefadrowil, pephaloglypin and sephalothin.

The adylating agent to be used in the method of this invention is an activated derivative of the side chain acid such as a lower alkyl (methyl, ethyl, n-propyl or isopropyl) ester or an amide. The amide can be unsubstituted in the --NH.sub.2 group which is preferred, or it can be substituted by one or two lower alkyl groups--identical or different--selected from the group two lower alkyl groups--identical or different--selected from the group two lower alkyl, ethyl, propyl and isopropyl. The derivative may be used in the form of a point for ourselected by the form of a point of a point of the budgeshier of the group loss. the form of a sait, for example, the hydrochloride or the sulphate. Examples or side diain asids are <u>Deplocylaly inc</u> or Depenydromyphenylglycine.

Examples of parent aring detailed take which can be adulated by the method of this invention are reaching distribution and e-ArA', this invention are reaching distribution and e-ArA', reaching description and e-ArA', reaching description and examined as the expression and examined as the example of the expression and examples are the example of 1-ACA and T-amino-3-bhliro-3-rephem-4-rarbowyl *De.

The amount of modulator to be added to the reaction mixture in order to the amount of modulator to be pends i.a. on the identity of the modulator and whilete the desired effect depends i.a. on the identity of the modulator and in the amount of equipment in the figures. It is thus important to notice can be found in the examples and in the claims. It is thus important to notice that a too high consentration of the modulator will prevent the desired that it are not included the or modulator in the reaction mixture is so low that it does not include the water activity in the reaction mixture. In any case, it will be lower than that of the reactions, preferably lower than 120 mM.

TEER:

The gravity to be used in the propose of this invention may be any equivconstruction of the construction of the constr WARTER Law, My to the english of antipolicy of the motive Mean terminal parent. Agricultures, e. C. E. et al. and the rest et, extraction as a description of the extraction of the ex

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In the protection of the equation of the equation of the property of the entropy Immopilização Estaveir mola (n. li <u>Goldyno</u>) is finamendially available from Blensinger Notation Manniesim Small, Sermany, under the trade name Endywell

TERE:

The solubility of the adplacing agent such as the <u>lepteng by the</u> or lepengue by the large as or a construction was trained to the control of the control of the construction of the construction of the control of the cont with the top sit. I to the read in resum, in an appear as eyetem as uses in the examples, the solubility of the hydrothloride of 1-rhenvialyaine amile is typically approximately 450 mM. However, the solubility is very dependent on the salt components in the solution, as well as on the pH value and the temperature of the solution. In some embodiments of the process of this invention, the initial reaction mixture is a slurry containing undissolved acylating agent and/or amino .beta.-lactam, which will dissolve partly or rully during the course of the readdish. The .beta. lastom ontibiotic formed may pre-digitate during the reaction and, also, the hydrolysis products of the anylating agent sime as https://www.and.leg-hydroxyphenylglypine, may precipitate. Hence, in some cases the reaction mixture will be a slurry throughout the duration of the reaction.

The amino .beta.-lastam, for example 6-AFA or 7-ADCA, used in the process of this invention may be obtained by enzymatic hydrolysis of the fermented peniodlins or rephalosporins ofor example peniodlin V, peniodlin 3 or rephalosporins of rephalosporins of the interpretability of the DOA and -- The control of the control of the control of the byte light of the control of solution of the used directly with un further purification or dilution.

PEPR:

Generally, the reaction temperature of the process of this invention may vary between about C.degree. C. and about 35.degree. C., especially between about 5.degree. C. and about 5.degree. C. Temperatures in the range about Didegree. -30. degree. C. may be preferred for convenient operation. The pH raine which is optimal depends on the type and purity of educate. Using makes which is optimal depends on the type and purity of educate. Using makes were still about 1.7 preferably in the range from about 0.1 to about 1.7 for the preparation of amomibility, a ye value in the range from about 6.8 to about 1.4 is preferred. Control of the pH value may be used. Suitable reaction rimes are from several minutes to several hours, in particular from about Learn to about a nours. Suitable storms concentrations may be from about 1 T ml to about 100 ml of the suit of supply and with, see below.

1818:

Terms the retiral are a final this invertible, whise ally him yields of the or the control of the terms on the first of the control of the first of the second of the content of th and the starting aming beta. -lastam, the pH value, the <u>enzyme</u> and the payerny and amount of modulators

1 11 13 1

D-HPGA is D-p-ny mowymenyl glycine amide, D-HPG is D-p-hydrowymenylalycine, e=ABA is += imin tenn Fill this aria, Amov is amovicillin, Thow is phenoxyagetic and, and invite promplate in a man

1919:

Violation Among the contract velocity of Among tenanting, and Visus. In 1988 to the contract velocity of 1988 formation, specified as unusualles minuting $\frac{1}{1000} \frac{1}{1000} \frac{1}{1000$

1 3.3 3 :

The following withinto not pentallin 3 advises attituty is used: the unit V of response to the amount of $\frac{1}{2}$ entropy that hydrolyses per minute 1 and mile of pentallin 3 under standard and tions (5) pentallin 3, 1.2M sodium prosphate kuffer, pH 3.7, 15.degree. 7 .

1 21 1 1 2

The ratio X is defined as the number of modes of THHE X insured per mode of Among provided for practical use this can be transformed to X storiles. THE X is the advantage of the advantage of the desired product and "modes X and is the moder amount of X and present in the reaction mixture. Thus, if X is this means that they desired synthesis takes place, no hydrolysis. If X is X, this means that X is near that twice as much X and X and X is present in the reaction mixture on a moder hasis. The ratio X can be calculated at any time during reaction, but in the following examples X is calculated at the reaction stop time, which is defined as the time at which X of the theoretical yield of X and X is present in the reaction mixture "based on the inserted amount of X and X are brackets are used to designate moder concentrations.

TEFF:

Retention times in minutes: 2.6 (D-HFG), 3.5 (D-HFGA), 5.0 ($\frac{6-AFA}{1}$), 13.5 (Amox).

TEFR:

In Examples 1-8 the following standard conditions for encymatic amovicilling synthesis have been used uses patent application No. WO 92/01061 for further strails :

1919 8 3

DEFF:

A standard synthesis immobilized penicillin 3 acylase from E. coli; encyme desind 8.6 T ml was carried out with no Bhox added. The Bhox level was 2.6 km. M in the reaction numbers due to a residual Fhox content of 2.2229 which the $\frac{1}{2}$ Thomas i. The small restriction is a complete in Table 1.

A standard synthesis immobilized penindllin (tanylase from E. poli; endyne dosing 8.6 T ml was carried out with no Ehyl added. The Fhox level in the reaction mixture was 0.6 .mu.M. The results are reported in Table 1.

TEPR:

From different immobilited Len 3 arylase preparations were used: at the bility is penintilled to applace from E. roll; thought desire for Toml; but are so rate form the total of the first to the contained from the rolls; the contained from the rolls; the contained from the rolls; the contained from the contained fro

1817:

Allings for A anylass proparations were distinct from Talkin them, art. Mo. whenever, was like Tomi, and from MBF, was fill Tomi. An energy desire of elements of most work employed in the two series. The results are required in Table 1.

1838:

A stantary synthesis from riline ipenibilling aboylase trong N. bull; encycle slip La. U mil was parried but with no Le τ -mandelib abid which The Fh w packer one level was also shown in the reaction rixture. The results detained are approximate on Table τ .

A standard synthesis becaminder Mannheim inmodilited penisilling applaye, experimental property of his objects of the Figure as a property of the first property of the free triangular level in the reservoir number of the first property of the

The top and disterred wimprive synthesis performance standard synthesis of fittings, incoming the penintiling transplaced in E. of hypersyne districtly for an incidence that when they are present in the reaction mixture in a comparation within the interval specifies, synthesis or the desired exclusive and antiquition is favoured as compared to hydrolysis of the application agent:

DEFC:

<u>Engyme</u> Antivity

DEFC:

Encymatic Synthesis of Amemicillin Using a Fixed Dosage of Immobilized Pen G Apylase and Marying the Phan Collectifation in the Reaction Mixture from 2.6 to 61.0 .mu.M

DEFO:

Enzymatic Synthesis of Amemibillin Using a Fixed Dosage of Immobilized Pen G Acylase and Varying the Phyl Consentration in the Reaction Mixture from SA. 9 to 127 .mu.M

DEPO:

Encympatic Synthesis of Americallin Using Various Immobilized Preparations of Fen S Acylase and Varying the Phox Concentration in the Reaction Mixture from $0.0015\,\mathrm{km}\,\mathrm{s}$

Encymatry Cynthesis of Americallan Using Varying Amounts of Encyme and χ Constant Conventration of Phox

DEFO:

<u>Murymatic</u> Synthesis of Amoxicillin by Using Soluble Pen G Acylase (Two Different Suppliers) and Varying the Phox Concentration in the Reaction Mixture from 2.6 ± 0.147 .mm.M

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Program of Systematic of Arthrotisch By March Irrabilitzet Den G.Anylase and Maryona to 18 metrators of 18 elementation of removed the 1881 mm

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<u>Minymatic</u> Synthesis of Americallin by Using Immobilized Pen 3 Acylase and Varying the 2-Thiophenesistic Acid Concentration from 2.25 to 2.3 mM in the Best in Mixture

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otik jimatu olikim tukotu oli ta Amerikon 1920. Motina dirima voline didenosti Aleydaye (and mario) ya Ma<u>liano</u> Motina di

TABLE 4

Figure | Initial velocity [Frow] | .mi.M.

Figure | Initial

 $(1, \sigma) = (1, \sigma) \wedge (\sigma + 1) \cdot (1, \sigma) + (\sigma + \sigma) \wedge (\sigma + \sigma) + (\sigma + \sigma) \cdot (\sigma + \sigma) \cdot (\sigma + \sigma) + (\sigma + \sigma) \cdot (\sigma + \sigma)$

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11.14.5

1. A method for providing a semisynthetic beta. -lagham antibiotic by <a href="https://www.netuc.com/netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.netuc.n estalyhed anylation of the parent obeta. Hactan with an amide or ester of the side chain acid wherein a modulator, which is a carboxylic acid of λ to λ : tark in at the, and is different from the reactions and the reaction product is also to the reaction mixture, at the beginning of the reaction process, it a neutron to the reaction process, it a

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MoDougall et al. <u>Broyne</u> Mibrob, Tephnol, 1961 vol. 4, pp. 114-118.

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The value of the outpoints of the inventor, are preferably salts with pharmaceutically asseptable inorganic in organic acids sich as hydrochloric avid, hydropromio avid, sulfurio avid, phosphorio avid, partario avid, vitali acid, fumaric acid, and the like.

B. H. B. :

In our rest to many of the corresponding free penitilline, the compounds of the invention are ejiliciently absorbed from the gastrointestinal tract and are then, under the incluence of encymes, rapidly hydrolysed to the corresponding free penicillins. This hydrolysis is an important teature of the compounds of the invention. It is assumed that the first step consists in a hydrolysis to the hydroxymethyl esters of the corresponding penicillins which subsequently decompose spontaneously to the free penicillins.

The compounds of the above formula VIIIa are new and can be prepared in Hirrorent numbers, for instance by reacting 6-animopenicillania acid with a oung outing the formula ##RIVIT## in which Risupil, Risupil, 2, and noare as writted state. The reserving is preferably performed in the presence of w. amine, e.g. triethylamine, and at room temperature or slightly elevated temperatures in an inertisal vent, such as dimethylformamide, whereby an intermediate of the formula ##EPVII## can be isolated which, after conversion to the group D into an unsubstituted of substituted amino group, yields the conversion of D can be performed as described only units of trimula VIIIa. The conversion of D can be performed as described tereinbefore. The grine group at the 6-position of the penicillanic acid can to, for is not horsestily, protested by well-known protesting groups, it is instance a trityle boug.

Amino Asia B.sup.2 n M.p. in OH-- Old-Ols O. I-valine -- O -- O. D.L-valine -- O -- Q. D-leadine OH.sub.3 .sub.2 ... OH.sub.2 ... D.Lisoleucine O.sub.2 ... OH.sub.3 ... OH.Sub.3

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...:

Frocess for the recovery of <u>anglorion</u> from a mixture containing <u>anglorion</u> and c-amonogenicallic acid <u>6-AFA</u>, in which a mixture of <u>amplorion and c-AFA</u>, with a pH higher than \mathbb{T}_r which apart from any solid <u>amplorion and c-AFA</u>, with a pH higher than \mathbb{T}_r which apart from any solid <u>amplorion being present</u> is homogeneous at a pH between \mathbb{T}_r and \mathbb{R}_r , is subjected to a pH lowering till a pH lower than \mathbb{R}_r . It reached, and the solid substance present is recovered. The process is in particular suitable to be applied to the heavy of numbers of the process is obtained after the <u>engymetric</u> adplation reaction of the process is in particular the <u>engymetric</u> adplation reaction of the process is a phenylogy time derivative as adplation agent. Pure <u>amplorion</u> can thus seconds:

BSFB:

The invention relates to a process for the recovery of ampicillin from a mixture containing ampicillin and 6-aminopenicillic acid (6-APA).

BOFR:

In the preparation of <u>amposition, with reals</u> being adviated with a <u>CDP-NES-F-Dish</u> decreasing up of the amposition and working up of the reaction mixture are account on several.

BARR:

A process for isolating the <u>ampliciblin</u> pure from a mixture containing anxiolilin and minor quantities of 6-AFA is described in IP+A-47030667. According to the process described in this Japanese publication, an acid aqueous mixture containing e-AFA and anxioliling is subjected to an extraction with butanel or isolamylal cohol, after which the pH is raised to a value to week r and I and the product is recovered by complete boiling down and therefore trying. The insweak of this method is that organic solvents that are stock I the process have to be added. In addition, complete boiling down and tree-re-drying is not insustrially practicable. Moreover, the process involves tomation of sales that are included in the tree-re-dried product.

HOLE:

OF-A-Fr4471 discloses a process wherein amproillin is recovered from a mixture of amproillin and amino-penicillanic and by conversion of the amproillin to the trialkylanine salt and recover the amproillin as instrialkylanine salt.

.

The specific transitive invention is to provide a simple, in fish mally practicable to rest as which <u>sticks</u> of to be recovered in pure form with it making use or said crumnic solvents that are alien to the process.

H375:

This is achieved according to the invention in that a mixture containing amproviling and d-AFA and having a pH higher than 7, which, apart from any solid amprojeling that is present, is homogeneous at a pH between 7 and 4.5, is supported to a pH 1 worths to a pH lower than 4.2, and that the solid superance present is to therei.

B.11 B:

In all of weight that by a weight the pH of the pixture to a value lawer than e.g., the characteristic rate of and σ , and particular retween 5.5 and 7.7, e.g., the characteristic rate of product of the control numerical, it be present to cause of products to the original and with a purity of more than σ mass σ , in particular more than σ mass σ , even if a large animal of $\frac{\sigma + \Delta F \Delta}{\sigma}$ is present in particular more than σ mass σ , even if a large animal of $\frac{\sigma + \Delta F \Delta}{\sigma}$ is present in particular more than σ mass σ . the mixture, after which it can be recovered. Besides <u>anxiotilin</u> the reaction now are often contains other valuable components, such as for instance the him are often pintains other valuable dimponents, each as in the consequently selected. In order to det a dimpercially attractive process it is consequently selected in the consequently are an included besent it has also been only train also to minimize the selected in the process of the process of the constraint of the constant of nystallines on virtually trapletely, efter which this mixture . The transfer of the second of the state of the second of t <u> Elejedi</u>t

The process according to the invention is in particular suitable to be applied 1011 in the working up of the reaction mixture which is obtained after the encypation anylation reaction in which $\frac{e-AFA}{e-AFA}$ is acylated with S-phenylaly time and e^{-AFA} is acylated with S-phenylaly time that is distalled invention can be installed as a starting number of that is distalled any starting property as e^{-AFA} . by submessively following, with isolation of impubilized encyme, the rouption mixture of an enlymatic adylation reaction parried out at a relatively high pH, ior instance a pH between .s and 15, in particular between 8 and 10, lowering the pH to a value between 7 and 9. Depending on the amount of <u>D-phenylglygine</u> (PG) formed during the acylation reaction, if desired, it is possible to remove first at a higher pH-value between 7 and \Re --which is selected dependent on the mixture such that already PG has been rrystallined out and ampicillin has not yet -- the eventually formed solid substance, which mostly will consist mainly of FG.

In an once end timent the scarting risture used is the misture obtained after an engine 12 acylarion reaction that ends at a relatively low pH, for instance an engine 12 and e.g., preferably between 7.5 and 6.5, and after isolation of a pH between 7.5 and 6.5. the solid substance which mainly contains the immobilized encyme and

the the scarting number of the initial cases and the initial contribution of the Alaman and the scart of the in partirol er sei 🕠

The pH may be lowered in several ways in the framework of the invention, i.i. instance chemically by adding an acid, for instance a mineral acid, in particular sulphuric acid, hydrochloric acid or nitric acid. Another possibility is for instance, if PSA has been used as acylatical acent in the lamplation beartion or if an ester of Follas been used and the \$H has peen Reft - arrow or to the control of the control of the control of the arrivation reaction, to
- not and any related of the arrow with amount a control of the arrivation reaction, to
- more the pH the company of the owner of amount a. Our able physical removal retulate are tor instable stripping with steam or an inert das; (steam) nstillation at the interior reserve, in particular thin-film evaporation; supporation in a spray tower; has receiving separation or electrodialysis.

The optimize pH at which amplituding is recovered depends in the composition of the optimize pH at which amplituding p in a separation of $\frac{-A_1A_2}{A_2}$ and $\frac{A_1A_2}{A_2}$ and $\frac{A_1A_2}{A_2}$ and $\frac{A_1A_2}{A_2}$ are the mass of the first $\frac{A_1A_2}{A_2}$ and $\frac{A_1A_2}{A_2}$ are the mass of the first $\frac{A_1A_2}{A_2}$ and the second of the $\frac{A_1A_2}{A_2}$ and the second $\frac{A_1A_2}{A_2}$ are the second of the $\frac{A_1A_2}{A_2}$ and the second $\frac{A_1A_2}{A_2}$ and $\frac{A_1A_2}{A_2}$ and $\frac{A_1A_2}{A_2}$

9 1 00 2:50 PM 2 of 5

the officer hand a high yield, which is addiened if the pH at which the affect of the photometric transfer which has been structed for the following the part of the period of the care time part of the period has a soft decay to the period be performed by the period well as the art of the art of the agy to determine the option of Holman proven with a time.

E018:

The process according to the invention for recovery of pure apply, lin in constitution with recording to the number of $\frac{1}{2} + \frac{1}{2} + \frac{1}{$

BOTE:

In trinciple any concept on he used that is suitable as catalyst in the conclusive and included are for instance the engines that are known under the deteral designations [penicillin amidase] and [penicillin acylase]. Examples of suitable engines are engines derived from Acetobacter, Aeromonas, Posiligenes, Alcaligenes, Aphanoclodium, Bocillus op., Cephalosporlum, Escherichia, Flavobacterium, Kluvvera, Mycoplana, Protaminobacter, Pseudomonas and Manthomonas, in particular Acetobaxter pasteurianum, Bacillus megaterium, Escherichia coli and Manthomonas citrii.

BOTE:

Preferably an immobilized <u>encyme</u> is used, since the <u>encyme</u> can be easily isolated and respect then. Immobilized <u>encymes</u> are known as such and are summercially available. Emample of suitable <u>encymes</u> are the Escherichia colingmy trom Baebringer Mannheim GmbH, which is commercially available under the name 'Encygel.FTM.', the immobilized Fenicillin-3 acylase from Recordati, the immobilized Fenicillin-3 acylase from Pharma Biotechnology Hannover, and an Escherichia colingenicilline acylase isolated as described in Wo-A-91/12781 and immobilised as described in EF-A-2214421.

BSFR:

The epopulation applied on reaction is mostly carried out at a temperature lower than or do need. 2., preferably between 2 and 28. degree. 3. The pH at which the supplied to applied its resultion is carried out is mostly between 5.5 and 13, preferably into when a and a.

H. 113:

In place the the <u>chargestic</u> acquartic reaction and the working up of the reaction mixture are mostly carried out in water. Optionally, the reaction mixture may also contain an organic solvent or a mixture of organic solvents, preferably loss than 30 vol. . Examples of organic solvents that can be used are alsohols with 1-7 carbon atoms, for instance a monoalcohol, in particular orthan 1 to other 1; a did 1, in particular others algorithm at trial, in tasticular solvers.

H. H. H. :

ESTT:

AMF1.3H.sub.L D=ampicillin trihydrate

4,2000

 $\label{eq:continuous} \mathcal{A} = \mathcal{A}^{T} \mathcal{A}_{T} + \mathbb{E} \left\{ \mathcal{A}^{T} : \mathcal{A}_{T} : \mathcal{A}^{T} : \mathcal{A}^{T$

.

主英国制作的过去式和过去分词

B 11 11:

13 1=11.01.1.1.1.1.1.1.0

1888:

Encymatic scupling of 200 sM of FGA and 200 sM of $\underline{M-AFA}$ at 8.degree. 2., tollowed by working up.

- :

A number of 40.0 for <u>TALA</u> and 50.0 do.f FHA was suspensed in eTO million was added to 10 go with and 50.0 million sediments. The restricting suspension was added to 10 go in with our follows Fig. 5 anylase from Bendrati Milano. This enoughers of number of a superior of wet enoughers, and the sediment of water and algorithms wet enoughers, and the sediment was according to restrict with 10 go in the water.

After L nours the pH had riven to hole, by beans of noncentrated agains as NH. subjective pH was brought to boe and after 8 minutes the reaction mixture was filtered through a SHB glass filter; the residue was washed with INT most water to degree. On . This residue was a mixture of engine and FG formed purious the reaction.

1835:

Encymatic scupling of 1.1 mM of PGA and 211 mM of 6-ABA at 5.degree. C., followed by marking up.

DEFR:

A mixture of 43.9 g of 6-AFA and 30.6 g of PGA was suspended in 877 ml of water and cooled to 5.degree. C. The resulting suspension was added to 100 g of [wet] immobilized Pon-3 acylase from Recordati [Milan]. This enzyme is connercially available in a mixture of water and glycerol ('wet_enzyme'); before use it was washed three times with 100 ml of water.

:EEF:

After thours the pH had risen to 3.10. By means of concentrated aqueous NH.sub.3 the pH was brought to 3.6 and after 5 minutes the reaction mixture was filtered through a 3-3 glass filter; the residue was washed with 100 ml of water [8.degree, 2.1. This residue was a mixture of encyme and PG formed during the reaction.

** ***

I. A probability of the small strain from a mixture containing amply thin and 0 -and open will be a wide v-AlA compression:

MER:

4. A process according to claim 1, wherein the mixture contains 2-60 mol $^{\circ}$ this, $\frac{1-60}{2}$ mol $^{\circ}$ to the total abound of $\frac{1-60}{2}$ and ampionizin.

JI.FR:

Fig. A process according to claim 1, wherein the mixture contains 8-80 mol $^{\circ}$ of $^{\circ}$ -APA, calculated relative to the total amount of $^{\circ}$ -APA and amprofilling.

to Approvious antiquity of air 1, wherein the provies curties comprises through 1 words the pH of a first 1, pullphase remaining after recovering satisfact till, as and recovering a second solid substance.

.11 F.F.:

II. A process for recovering $\frac{\text{apply}[1][in]}{\text{trom a mixture containing }\frac{\text{ampivilling}}{\text{transform}}$ and \mathcal{C} -units projection and $\frac{\text{transform}}{\text{transform}}$

1188:

II. Additionary arteriated to district , where in the sample of reaction is $\frac{1}{2}$

11 : : :

1). A prover carrier summer of air 11, wherein in the <u>embyrator</u> anylation reaction the pH of raintains to you not liet a spirit in of any miles and wherein walk is turing the pH of air to mplished by removing armonia.

11.1111:

prividing the ristore syntaining application and ϵ -AFA, said mixture nating an initial pH dreater than T and desire his general at a pH detween T and Fig. application present; and

. We find the unitial $j \in \mathbb{N}$ the purture to a $j \in \mathbb{N}$ value and we just an interpretable H

obtaining a mixture containing $\frac{ampicul.in}{and}$ and $\frac{b-amino}{b-amino}$ penicillin that is prepared from the reaction mixture of an $\frac{b-amino}{b-amino}$ adulation reaction in which $\frac{b-appa}{b-amino}$ is adulated using D-phenylglycineamide (PGA, or esters of $\frac{b-amino}{b-amino}$ said mixture having an initial pH greater than T; and

reducing the pH_{ij} (s with righture and organization, our <u>ampirition</u>,

Generate Collection

11*: Entry : 11

o negotration of a greating agent plus detailed an derivative of at least 40

ABFL:

.beta.-Laptam derivatives are synthesided by an engymatic reaction of the garent arine thera. -last are with the corresponding advlating agent, the The contraction of the anything agent plus the contentration of thems. -labtam derivative in the reaction rightly's being above about 400 mm.

BSER:

This invention relates to a process for the preparation of .beta.-lactam derivatives by ensymmatic adylation of the parent amino .beca.-lastam with an adylating agent. The amino lbeta.-lastam may be $\frac{6-aminopenicillanic}{16-APA}$, 7-aminodesasetoxysephalosporanic acid (7-ADCA), T-amino pophalosporanio abid T-ACA) or T-amino-3-phloro-3-pephem-4-parbowylate and the anylating agent may be a derivative of <u>D-phenylalypine</u> or (-p =h.yar myg neny, 1.7 tine.

1-211-1

Today, semisynthetia .bota.-laptams such as <u>Ampibillin,</u> Ampxibillin, Caiadlor, Sephalewin, Sephadrowil and Sephaloglysin are prepared in industry by shemical methods, for example by reacting an amino .beta.-lactam such as k-aminopenisillaris asid, usually having its carboxyl group protested, with an assivated side shair derivative, followed by the removal of the protecting group by hydrolysis. It is important due to, for example, yield, that the uning .beta.-labtam, for example d-AFA, is used in a pure, dry form, presenting (American), for example property is used in a party, or recently presenting in a parity higher than 90. For example, Ampiculling (40-2-1) present property is set amidopenical large acid; can be prepared by reacting (FAR), having a least able protected carboxyl group, with property involve acid this price, followed by removal of the protecting group by hydrolysis. These resulting typically involve costly steps such as sub nero Figure Tylons confinions and Drami's solvents like methylene chloride and Contract to the Contract of th

BSEB:

Horrature production of <u>ApproxIII.n</u> from pure <u>*-AFA and a D-phonylgly ine</u> derivative soom as a lower alkyl ester is known from Mest Berman patent application nature publication No. 144, but the product application No. 144, but is different application favorable for the product application favorable for the product application having publication in the prior are have typically used to be made or the <u>D-pu by plytone</u> derivative and below of mM of <u>*-AFA</u>, the highest visible reported was of a European patent application having publication No. 44, justs.

BSTB:

The arm other at Flavor crum as $\frac{e-AiA}{e}$ is a prompty project in $\frac{e-AiA}{e}$ in a property of the interpretable maps of a fearence is $\frac{e-AiA}{e}$ in a rewardle periodillim. The periodillim of t . The control of the

10 -. on M. The character and an experimentarious stallines to detail pater x-Aig or -Ai W. In the -Ai W. Mare, the immented penintlin have been through another process set restnessly in a step ...

Build:

The protential drawbaths of the known enoughts methods for production of Amproplish. Answerillin and Dephaloxin none have yet been upscaled to industrial applicability are the high bosts yield lisses and investments to the necessary unit specification in three when the amino detailed at the contact of production and petite sector used as raw material for the reaction described as the material for the reaction of the pressure very live typically less than 5. mM , thus described as as a sector of the pressure the description of another yield in the property of materials of Amproviding as described as.

BOTE:

A process for $\frac{\partial L_{2} \nabla L_{1} + 2}{2}$ synthesis of Anomabilia is described in Agric. Buil. Them. 44 late $\frac{1}{2}$, but et seq., which process is performed in a reaction medium containing L_{1} of time volume or more of depropanci and L_{2} volume volume of their alsohols. When the last mentioned alsohols or L_{2} of the rappear is seq, the initial processing of the starting of the starting materials, leading L_{2} is very low, i.e. It and if L_{2} is respectively. When L_{2} or L_{2} represents is used, the initial concentration of the starting materials, L_{2} alpha. L_{2} (p-1, droxyphenyl) glycino mothyl ester and L_{2} and L_{3} is 460 and 230 mM, respectively. It is stated in this paper that the addition of more than 100 mM of L_{2} alpha. L_{3} (p-hydroxyphenyl) glycine methyl ester and of more than 50 mM of L_{3} alpha. L_{3} (p-hydroxyphenyl) glycine methyl ester and of more than 50 mM of L_{3} alpha. L_{3} (p-hydroxyphenyl) glycine methyl ester and of more than 50 mM of L_{3} and L_{3} in the publication reaches away for increasing the superior is that this publication reaches away for increasing the superior L_{3} is the start his publication reaches away for increasing the reaction risks.

BSPE:

After the effective filing date of the application for a patent on this invention, namely Sep. 18-21, 1990, a poster was published at a NATO Workshop. The poster dealt with the preparation of dephalosporins and, according to this poster, working at low temperature had several positive effects on the issue in. The hiddent of neutration of anylating agent used by this work was a DEM of 1-, application by the recipions setting as there was no indicate not the poster and principle which is to the poster and principle within agent.

BSFR:

It has now, surprisingly, been found that the yield in the encymatic preparation of .beta.-lactam derivatives can be improved by carrying out the reaction at high concentrations of the acylating agent.

BREE:

F, the process of this invention, of is possible and attractive to use a profession of the acts. Let all for a wample $\underline{\cdot}$ -AFA or $\overline{\cdot}$ -AFCA, without affine in 1 sectors as for a stable that, for example $\underline{\cdot}$ -AFA or $\overline{\cdot}$ -AFCA, Suring positivation and or is later steps is thus avoided, and investments in positivation equipment the former was a positivation equipment former used for isolation of $\underline{\cdot}$ -AFA is weak for isolation of Approximation. Amountaining and Tephalewin.

B.11 B :

Advantage custy, the high yield act office to this invention can be obtained without the twent of a lower propagation contains a lowest season this contains as $\frac{1}{2}$ where only one of the lower problem was obtained at $\frac{1}{2}$ and $\frac{1}{2}$ where $\frac{1}{2}$.

B.317 B.3

Annual navy, this inventor provides a provest for enignation that to be 1 about a number as the provided provided provided by the 1 about a second provided by a derivative or 1 about 1 about 1 about 1 about 2 about 2 about 1 about 1

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In the aspect, this process is characterized in that the contentration of the contentration and contentration of the ready is a contentration of the aspect of the contentration of the ready is a contentration of the process of the contentration of the statistic process is characterized in that the initial contentration of the statistic mainstrates about 101 mM, more preferred above about 101 mM, more preferred above about 101 mM. In a still further aspect, this process is maissterized in that the initial amount of the adulating agent, for example, the 1-pleny slyvine or 1-pleny representable about 101 mM. In a still further aspect, this process is maissterized in that the initial amount of the adulating agent, for reaction mixture about 102 mM. In a still further aspect, this process is maissterized in that the initial amount of the reaction mixture about 102 mM above the solubility of said agent in the reaction mixture preferably above the solubility; or the initial amount of the advising agent in the reaction mixture preferably above the solubility of the advisting agent in the reaction mixture the initial amount of the amino operation agent in the reaction mixture the initial amount of the amino operation agent in the reaction of advisting agent plus the concentration of obstation as a still further aspect, this invention relates to a process whereby the concentration of advisting agent plus the concentration of obstation mixture is above about 500 mM, more preferred above about 500 mM, even more preferred above about 500 mM. In an additional aspect, this invention relates to a process whereby the initial concentration of advising agent in the reaction mixture is above about 500 mM, even more preferred above and the first mM, more preferred above about 500 mM, where preferred above about 500 mM, where preferred

Examples of theta. -lastam derivatives that may be produced by the process of this invention are Amposittin, Amonibillin, Cefactor, Cephalexin, Cephadroxil.

owną,

The adviating agent may be a derivative of <u>D-ph-pylylydine</u> or D-p-hydroxyghenyldlydine such as a lower alkyl (methyl, ethyl, n-propyl of us propyl estern of an amide which is unsubstituted in the --CONH.sub.l group. The advisers of the beginning may be used in the form of a salt, for example, the Holl salt of the H.sub.l St.sub.4 salt. The adviating agent may be added in an active form of the active form may be formed in situ.

PEFR

The entropy to be used in the process of this invention may be any theorem satalyzing the reaction in guestion. Such shippes have frush shipse siller as well for example, termed periodilin amidase or peniodilin applace and classified as E.C. (E.D.). I.E. number of microbial solution and process are shown to have this activity, behaved from the example Rose spacer, sandament, Myoglana, is taminabased, Aeromonas West Jerman patent application having publication Mo. (1980). Paculation having patent Mo. (Above , Flav hasterium lut in patent application Mo. (1981) and publication Mo. (1981). Actobacter pasternianum, Baccillus megaterium, Manthemenas citrii (European patent application having publication Mo. (1981), Wanthemenas citrii (European patent application having publication Mo. (1981), Wallywera citrophila (Aar. Biol. Chem. 37 (1973), 0007-1894) and Formerichia coli West Gernan patent application having publication Mo. (1983), U.A. The Formerichia coli engage is commercially available. The engages also ray is a second coli application hydrolase, acylase or amidase. In this came up, the color, interesting maintenance of Bakke to Former School, Classic, C

1818:

in it is proprietable to the company of the a respective form, it is example, see Untraples of the distress of in. The district may be disedy any an wholeth district British Experience of the compact of the property and the compact of the Marrheim Smill, Jermany, under the trade name Encygel.

The solubility of the adylating agent such as the <u>Tephenylglycine</u> or Tepenyle appaenylalycine derivative will vary with the identity of the depictative and activitie composition of the reaction for a which is a percent of the Element of the example of the condition of the Element of the example of the condition of <u>Têrnanyana sur anaka anaka anaka anaka ang menakanya kan atènya anaka Hisebyer, tab</u> Kanahanya ya vyiya kajendenta in tabahsali ja pronepis jihotne salika ing kesaka. as in the pH value and the temperature if the solution. In sime embidiments if the process of this observious, the unitial reaction mixture is a slurry containing uniiss lived adylating agent and or inetal-lastam, which will dissolve partly or fully during the course of the reaction. The ibetal-last am turned may presign ate liming the reading and, also, the hybolysis products of the advisor of spent such as <u>leptonium, the</u> and lepeny mixyment divides, may precipitate. Hence, in many cases the reaction mixture will be a slurry the raginaum the least out.

The amino theta.-lastam, for example $rac{6-ALA}{2}$ or U-ADCA, used in the probess of this invention may be obtained by enzymatic hydrolysis of the fermented penicillins or cephalosporins, (for example penicillin V, penicillin G or bephalosporin 0: br their ring enlarged analogues (for example V-DCA and G-DCA) or derivatives thereof followed by removal of the hydrolysis by-product, if desired (phenoxyacetic acid etc.). Advantageously, the crude solution can be used directly without further purification or dilution.

: EEF:

Senerally, the reaction temperature of the process of this invention may vary between about Cliegree. S. and about 35.degree. C., is especially between about 10. degree. 1. and about 30. degree. C. Temperatures in the range about . .degree.-30.degree. C. may be preferred for convenient operation. The suitable pH value depends on the type and purity of mayne. Using Escherichia boli encyme, the pH value is typically in the range from about 5.5 through about 7.5, preferably in the range from about 6.1 through about 7. For the preparation of Americalian, a pH value in the range from about 8.5 through lately 4.4 is properted. Threshof the pH value may be used. Suitable reaction times are in mesoveral minutes to several hours, in particular from about 1 2 non to about a nours. Our able onlyme with surprations may be from about 1 Holabour 19 of million and mit Tijen med at ivity, see below'.

DEFR:

Using the process according to this invention, extraordinary high yields can pe obtained. The high yields are obtained using the teachings of this invention and properly selecting the concentration of the adylating agent, the ratio between the confentration of adylating agent and the starting amino .ceta.=lastam, the pH value and the encyme.

As become to a superconduct of anylogs activity the full wind is used to the dult of supersymmetric the absence of <u>engine</u> that hydrolyses per minute 1 .mu.mule pentalling funds of an arise to undistribute to pentalling 7, 0.2M Sadium phasphare into the pentalling of the pentalling of the sadium phasphare. buffer, pH value to , of degree. To .

1717

And the bound of the <u>crafts</u> and the Boundary tendent point as in given by the tendent of the contract of the An entropy of the control of the con 9-1-2-1-2-1-2

Came and accompanion Example I, only I only Hall Wile used instead of <u>pthin</u>. There there a name on Sephalemin Ly distance and the naw, y.e. is a father at an inceptance on extrations of I = 1 Main Life of the Came who who in table as

TEL mm (-AFA) and Too mm I-FWA sulphate sult are adjusted to a pH value as Unitive--a in rable by and the <u>encymatic</u> synthesis is carried out at 21, degree. To and pH states nations, total volume 2 bi and TOO T solable <u>encyma</u> from

The profile with 18 or Move-AlA and \sim 10 MeV. However, if the line v , 4 and v = 0 solution $\frac{v_{\rm B}}{v_{\rm B}}$ from Escherichia bill obtaing victors; i.e. all and running the synthesis. Temperatures as indicated in Table 4, the maximal yields of <u>Amproclust</u> ontained are shown in Table 4.

1777

This example was performed analagously with Example 1 using D-BBM instead of THE MAIN like magnitude yields of $rac{Employ}{2}$. $rac{Employ}{2}$. $rac{Employ}{2}$ in Table 7.

Ben Wigartly por true from temperation protocy distriction, extraction int nuryl average and case into an agueous phase resoluting in a solution of sweightorolume open V is hydrolysed by Semacylase.TM. (immobilized pen V acylase from Novo Mordisk $\tilde{A}/S)$ at a pH value of 7.0. The phenoxyacetic acid is removed by excraction and to the resulting $\underline{\theta-APA}$ (150 mM) solution, containing minor amounts of biproducts from degraded pen V and 6-APA, is added 45 0/mlsoluble engyme from Escherichia coli and D-FGA (to a final Concentration of the pH value is adjusted to 6.4 and the reaction is allowed to rrupewa at Lô.awbree. To keeping the pH dalue constant.

1. E.I. R :

Under these conditions a total of 130 mmole of $rac{Ampicillin}{2}$ (90) is formed per liter of reaction volume.

Description was mixed with a solution of $\frac{c-A+A}{c-A+A}$ and D-FDA to a total volume of 25 ml the resulting risewise containing 13 mM $\frac{c-A+A}{c-A+A}$ and the mM D-FDA, having pH value +.1 and *publication at the resulting photon was allowed to produce to H state or mixed as the containing the containing the state of the containing the state of the containing the containing

A mixture of 96f mg c-APA and 3018 mg HFGA in water is adjusted to pH 6.2 at 15.degree. 7. and 1656 T soluble penicillin 3 acylase from E. coli is added to a final volume of 19.5 ml. The synthesis is allowed to proceed at constant temperature, using 1M synthesis and to seep the pd at c... After 17.6 is not the resemble normal size of the peak to be seen to a yield of the case to be the resemble to a yield of the case to be the resemble to a yield

1848:

The massimble peninclian analysase trom E. boli is added to a mixture of $\frac{1}{2} \frac{1}{2} \frac{1$ The manufacture of the second of the control of the captain, the second of the control of the co

Therefore with 10 ord ϵ -AFA, 400 mM HF WA, 165. The left be periodilling anylose from F. with, 140 cm. Archibilling and was profibed after 5 hours, when the reaction was carried out at μ H 0. Table at τ 0. The profibed

Page conditions as described in example γ using 20 and ϵ -AFA and 400 am HF Ξ

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regulated in the community of the effect Archival II in after the ere-
1 811 3:
out...
K-ABA is c-aminopeniciliano a min, M-ADVA is M-aminodesa setomy rephalosporanco
abid, D-BBA is D-phenylgiyoinamide, DEGM is D-phenylgiyoin methyl ester, M-DVA
is T-yhenowya setahidodesa betowy pephalosporanio acid, 13-20A is
 Texhenylaretamiusdesasetsmysephalssporanis asid and HPSA is
iełeny m czypneny, ny miamilie.
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 <u>Programs o</u> wystawiwa i P<u>Apisa (1111)</u>,
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Encymatic synthesis of Amowicillin.
 DEPU:
 Enzymatic synthesis of Amoxicillin.
 Encymatic synthesis of Amowicillin.
 ......
Referrich fines in minutys: 4.1 | Depoty 6.3 (C-ADCA); 9.1 (<u>K-APA</u>); 9.1
  D-FGA1, 19.4 [D-ghalewih]; 13.9 (<u>April:111n</u>); 18 (D-FGM).
 DEFV:
 Retention times in minutes: 2.8 (D-p-hydroxyphenylqlysine); 3.3 (HEGA); 5.4
  .6-<u>A9A</u>); 13.2 (Amoxidillin).
 . . . . .
                                                      namimum yield reaction time, mM
 TABLE 5
 reaction time, my hours
  1. In the problem for the preparation of a liberal-labtam amide comprising
 guidenting a nearly gold med this the stop conditing of a period in,
 Teaming messeromy reginal sportanic acid, Teaming rephalosporanic acid and Teaming messeromy reginal sportanic acid, Teaming rephalosporanic acid and Teaming messeromy in the spin messeromy late to an <u>engagnation</u> respection with an acyllating agent in a practic morimomy containing less than Fourthment volume acyllating agent in a practic morimomy containing less than Fourthment comes
 or .-Euranol or the .beta.-lastam amide is amoximillin and the adylating about is be.alpha.-.p-hydroxy-phenyl) alycine methyl ester, the improvement
  is a transposition for the day of the first of the solution agent and the abera. Hastan
Comprising using a consent stion of the application agent and the abera. Hastan
 amide in the reaction mixture greater than 400 mM and the encyce is derived than a rich organism selected inch around the state of Escherichia coli,
 Abstribation pastsurgarum, Manthonomas outrii, Kluyvera ditrophila, or Pacillus
 product of the latest
  1115:
  where the arithmeter of are the first the arithmeter +1 and +1
  <u>y-amin'nyani dillahin anii.</u> T-amin'iks wet awyoephalosporanin anii.
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Hamunior phase operation apparent the among the oblight Hermograph (44 hard) wystatos

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To A process according to plain I or u, wherein the applating agent is <u>lepoenylalyzone</u> or Defenydrowyphenylglyzone or derivatives thesest.

e. Application and application caused on a large material and section of the sect on wind the life of Monte, it and the representation of the monte, and

In. A process agnording to claim I or I, wherein the concentration I the aming theta. -lastam in the reaction mixture when the entymatic reaction starts is in the range from about 50 to about 750 mil.

on. Dr. A process as ording to blaim I or ., wherein the concentration of anylating agent in the reaction nimbure when the endynamic reaction status is greater than 400 pM.

11. A process according to claim 10, wherein the concentration of the anylating agent in the reaction mixture when the enguments reaction starts is greater than Til mM.

27. A process according to plaim 1 or 2, wherein the amount of the acylating solubility of the agent in the reaction mixture.

us. A process according to claim 1 or 1, wherein the amount of the adylating agent in the starting reaction mixture is greater than half the amount of said agent which is soluble in the reaction mixture plus the amount of the amino-.beta.-lastam in the reaction mixture when the enzymatic reaction starts.

33. A process according to claim 1 or 2, wherein the encyme used is classified $\frac{1}{2}$ is Ed 3.5.1.11.

the April 1988 and rainable claim I or a, wherein the energy used is able to hydrolyce penintuon ito ing<u>a</u>eth site

35. A process according to plaim 1 or 0, wherein an <u>encyme</u> in reusable form is ...

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er. A promess arm time to claim form, wherein the <u>enguese</u> reaction is